

DELAWARE HOSPITAL ISSUE

DELAWARE STATE MEDICAL JOURNAL

Official Organ of the Medical Society of Delaware

INCORPORATED 1789

VOLUME 31

FEBRUARY, 1959

NUMBER 2

RETROPERITONEAL HEMANGIOPERICYTOMA

Complete Contents on Page iv

For a quick comeback

V-CILLIN K[®]

(penicillin V potassium, Lilly)

*provides dependable, fast,
effective therapy*

In tablets of 125 and 250 mg.

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EFFECTIVE AGAINST MOST STRAINS OF STAPHYLOCOCCI
CHLOROMYCETIN[®]
COMBATS MOST CLINICALLY IMPORTANT PATHOGENS

Surveys of *in vitro* performance of various antibiotics over the past several years indicate a definite decrease in activity against the staphylococcus.^{1,2} CHLOROMYCETIN, however, continues to demonstrate a high degree of potency against this stubborn pathogen.¹⁻⁴ Even the strains responsible for hospital-acquired staphylococcal infections, which are resistant to most other antibiotics, may be sensitive to CHLOROMYCETIN.⁵⁻⁹ For this reason, it has been recommended for immediate use in suspected staphylococcal infections in infants, their mothers, and in surgical patients.¹⁰

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CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

REFERENCES: (1) Holloway, W. J., & Scott, E. G.: *Delaware M. J.* 30:175, 1958. (2) Roy, T. E., et al.: *Canad. M.A.J.* 77:844, 1957. (3) Markham, N. P., & Shott, H. C. W.: *New Zealand M. J.* 57:55, 1958. (4) Royer, A., in Welch, H., & Marti-Ibañez, E.: *Antibiotics Annual 1957-1958*, New York, Medical Encyclopedia, Inc., 1958, p. 783. (5) Blair, J. E., & Carr, M.: *J.A.M.A.* 166:1192, 1958. (6) Caswell, H. T., et al.: *Surg., Gynec. & Obst.* 106:1, 1958. (7) Fekety, F. R., et al.: *Am. J. Pub. Health* 48:298, 1958. (8) Godfrey, M. E., & Smith, I. M.: *J.A.M.A.* 166:1197, 1958. (9) Kessler, A. D., & Scott, R. B.: *J. Ped. Child.* 96:294, 1958. (10) Shaffer, T. E.: *J. Michigan M. Soc.* 57:851, 1958.

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IN VITRO SENSITIVITY OF PATHOGENIC STAPHYLOCOCCI TO CHLOROMYCETIN AND
TO ANOTHER WIDELY USED BROAD-SPECTRUM ANTIBIOTIC FOR 1958, 1957, and 1955*

1958 (200 STRAINS)

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ANTIBIOTIC A 37.5%

1957 (200 STRAINS)

CHLOROMYCETIN 94.0%

ANTIBIOTIC A 61.0%

1955 (42 TO 103 STRAINS)

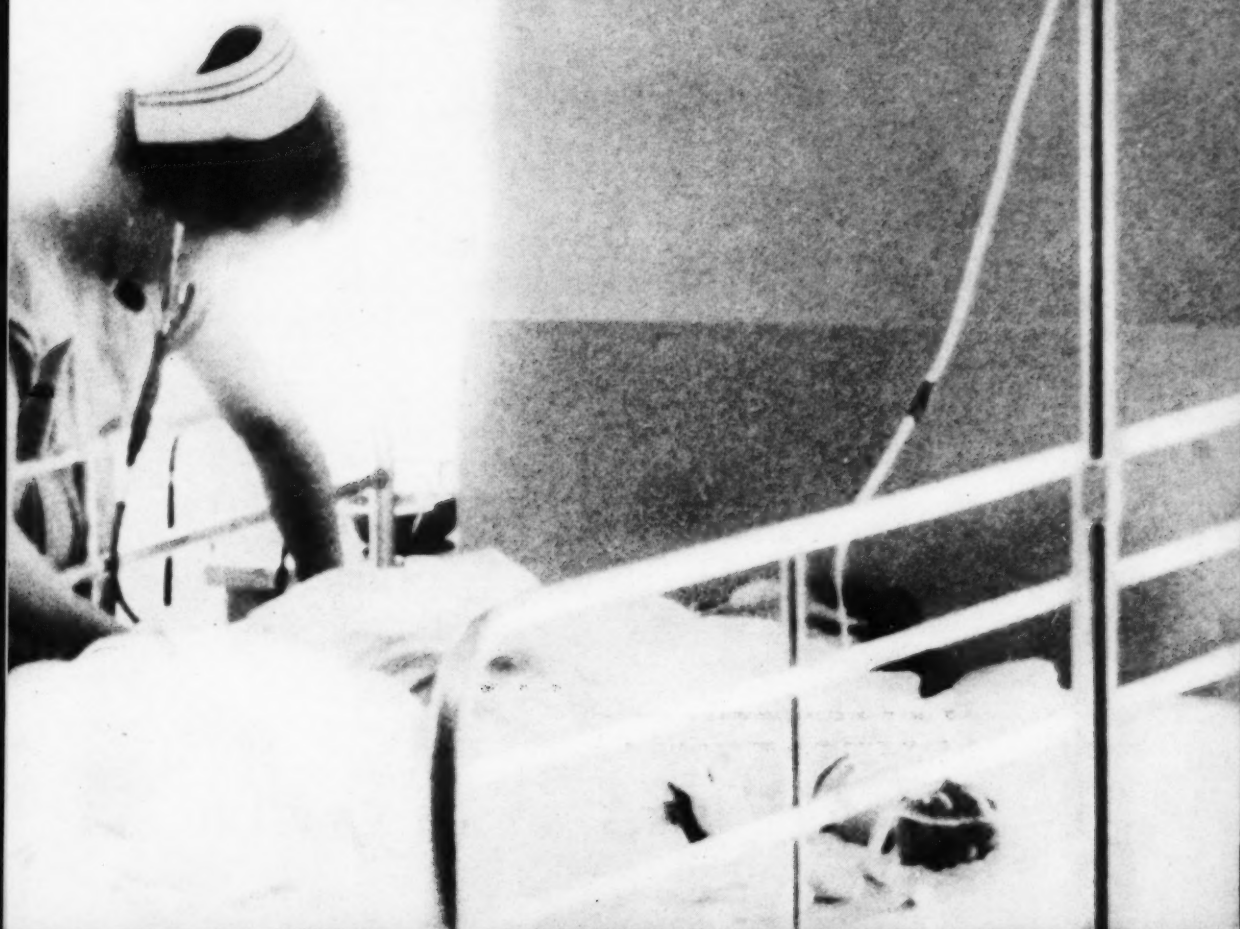
CHLOROMYCETIN 98.0%

ANTIBIOTIC A 69.5%

0 20 40 60 80 100

*Adapted from Holloway and Scott.¹ In this study CHLOROMYCETIN
and Antibiotic A were used in identical strengths of 5 mcg.

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Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, Published by the American Medical Association, Chicago.

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Subscription price: \$5.00 per annum, in advance. Single copies, 75 cents. Foreign countries: \$5.00 per annum.

Entered as second-class matter June 28, 1929, at the Post Office at Wilmington, Delaware, under the Act of March 3, 1879. Editorial Office: 1618 N. Broom Street, Wilmington, Delaware. Business Office: 621 Delaware Avenue, Wilmington, Delaware. Issued monthly. Copyright, 1959, by the Medical Society of Delaware.

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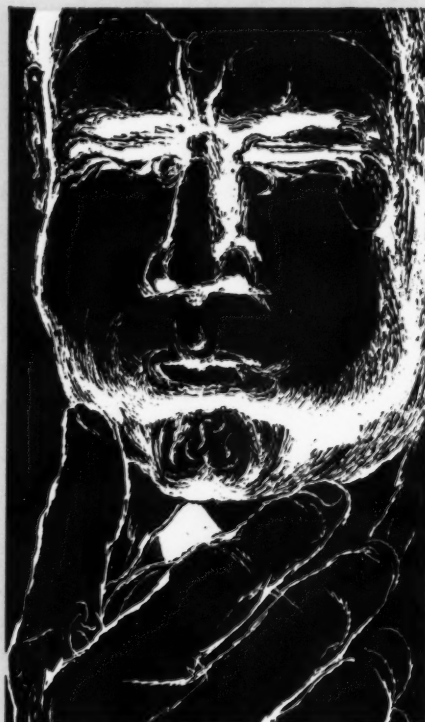
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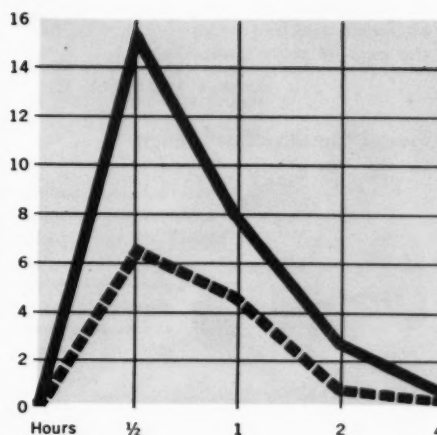
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Units/cc.



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Note the high upper levels and averages at 1/2 hour, and at 1 hour.

Doses of 400,000 units were administered before meal-time to 40 subjects involved in this study.

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Now—All cold symptoms can be controlled



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Provides well-tolerated APAP (N-acetyl-p-aminophenol) for prompt and effective analgesic and antipyretic action to make the patient more comfortable.

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[†]Lhotka, F. M.: Illinois M. J. 112:259 (Dec.) 1957. Fabricant, N. D.: E. E. N. T. Monthly 37:460 (July) 1958. Farmer, D. F.: Clin. Med. 5:1183 (Sept.) 1958.

Special "timed release" design



first—the outer layer dissolves within minutes to give 3 to 4 hours of relief

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also available for those patients who prefer liquid medication: Tussagesic suspension

Each TUSSAGESIC tablet provides:

TRIAMINIC®	50 mg.
(phenylpropanolamine HCl)	25 mg.
pheniramine maleate	12.5 mg.
pyrilamine maleate	12.5 mg.
Dormethan (brand of dextromethorphan HBr)	30 mg.
Terpin hydrate	180 mg.
APAP (N-acetyl-p-aminophenol)	325 mg.

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FOR RELIEF OF ANXIETY
AND MUSCLE TENSION

Selective

Does not interfere with autonomic function

Does not impair mental efficiency,
motor control, or normal behavior

Has not produced hypotension,
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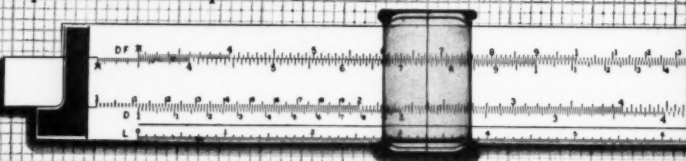


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(triacetylsclerandomycin)
Capsules / Oral Suspension

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* designed for
superior control of
common Gram-positive
infections



in the
patient:

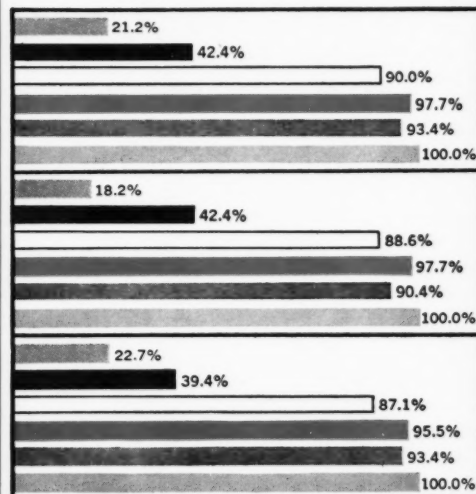
95% effective in published cases¹⁻³

Conditions treated	No. of Patients	Cured	Improved	Failure
ALL INFECTIONS	558	448	80	30
Respiratory infections	258	208	31	19
Pharyngitis and/or tonsillitis	65	58	5	2
Pneumonia	90	66	17	7
Infectious asthma	44	38	—	6
Otitis media	31	29	2	—
Other respiratory (bronchitis, bronchiolitis, bronchiectasis, pneumonitis, laryngotracheitis, strep throat)	28	17	7	4
Skin and soft tissue infections	230	191	38	1
Infected wounds, incisions and lacerations	41	33	8	—
Abscesses	51	43	8	—
Furunculosis	58	51	6	1
Acne, pustular	43	28	15	—
Pyoderma	19	19	—	—
Other skin and soft tissue (infected burns, cellulitis, impetigo, ulcers, others)	18	17	1	—
Genitourinary infections	28	19	3	6
Acute pyelitis and cystitis	10	8	2	—
Urethritis with gonorrhea or cystitis	8	8	—	—
Pyelonephritis	4	1	—	3
Salpingitis	5	1	1	3
Pelvic inflammation with endometriosis	1	1	—	—
Miscellaneous (adenitis, enteritis, enterocolitis, subacute bacterial endocarditis, fever, hematoma, staphylococcus carriers, osteomyelitis, tenosynovitis, septic arthritis, acute bursitis, periarthritis)	42	30	8	4

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against resistant staph

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ON 130 STAPHYLOCOCCI*



Antibiotic A 2-10 units TAO 2-15 mcg.
Antibiotic B 5-30 mcg. Antibiotic D 2-15 mcg.
Antibiotic C 5-30 mcg. Antibiotic E 5-30 mcg.

Percentage of organisms inhibited by the range of concentrations listed for each antibiotic.

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Highly palatable—"practically tasteless" active ingredient in a pleasant cherry-flavored medium.

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References: 1. Koch, R., and Asay, L. D.: J. Pediat., in press. 2. Leming, B. H., Jr., et al.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 3. Mellman, et al.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 4. Olansky, S., and McCormick, G. E., Jr.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 5. Shubin, H., et al.: Antibiotics Annual 1957-1958, New York, N. Y., Medical Encyclopedia, Inc., 1958, p. 679. 6. Isenberg, H., and Karelitz, S.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 7. Wennersten, J. R.: Antibiotic Med. & Clin. Therapy 5:527 (Aug.) 1958. 8. Kaplan, M. A., and Goldin, M.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 9. Truant, J. P.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958.

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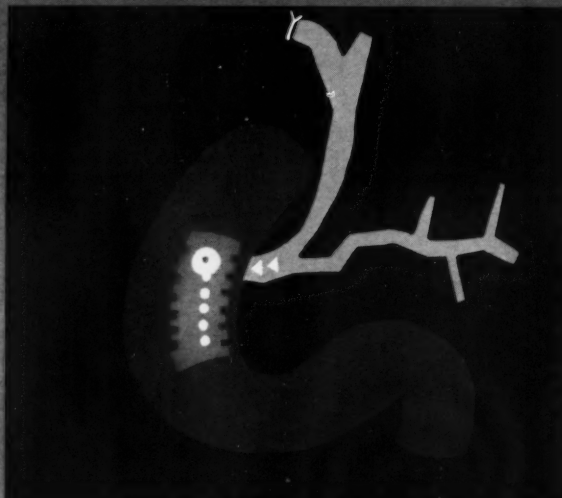
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Source: Vazquez, S. G.: J. Internat. Coll. Surgeons 28:394, 1957.

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Hyoscine hydrobromide ..	0.0065 mg.
Phenobarbital (1/4 gr.)	16.2 mg.

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1. Bickerman, H. A.: *In* Drugs of
Choice 1958-1959, ed. by W. Modell,
Mosby, St. Louis, 1958, p. 562.

2. Hayes, E. W., and Jacobs, L. S.:
Dis. Chest 30:441, 1956.

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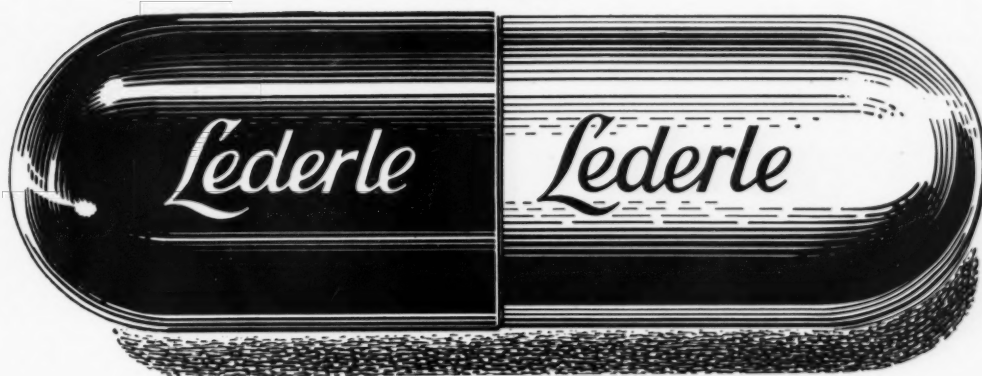
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Reinhardt, D. J.:

Delaware State Med. J. 30:1, January 1958.

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Ohio State Med. J. 54:1168, September 1958.

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Herrmann, G. R., Hejtmancik, M. R., Graham, R. N. and Marburger, R. C.:

Texas State J. Med. 54:639, September 1958.

dosage: one 250 mg. tablet DIURIL b.i.d. to one 500 mg. tablet DIURIL t.i.d.

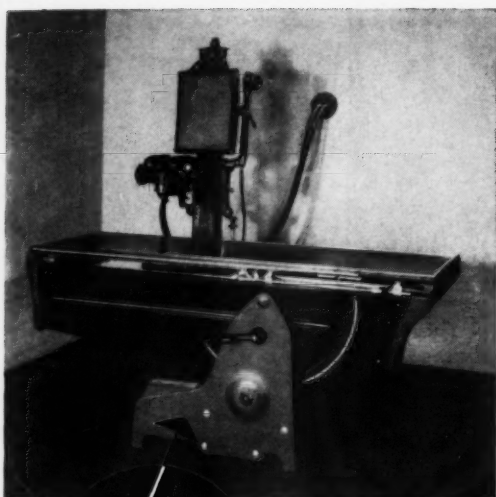
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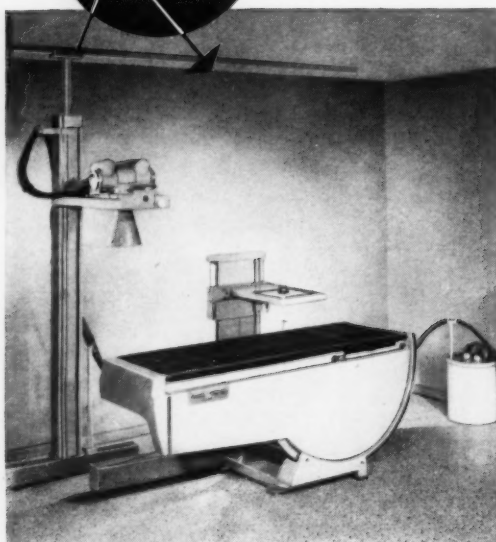
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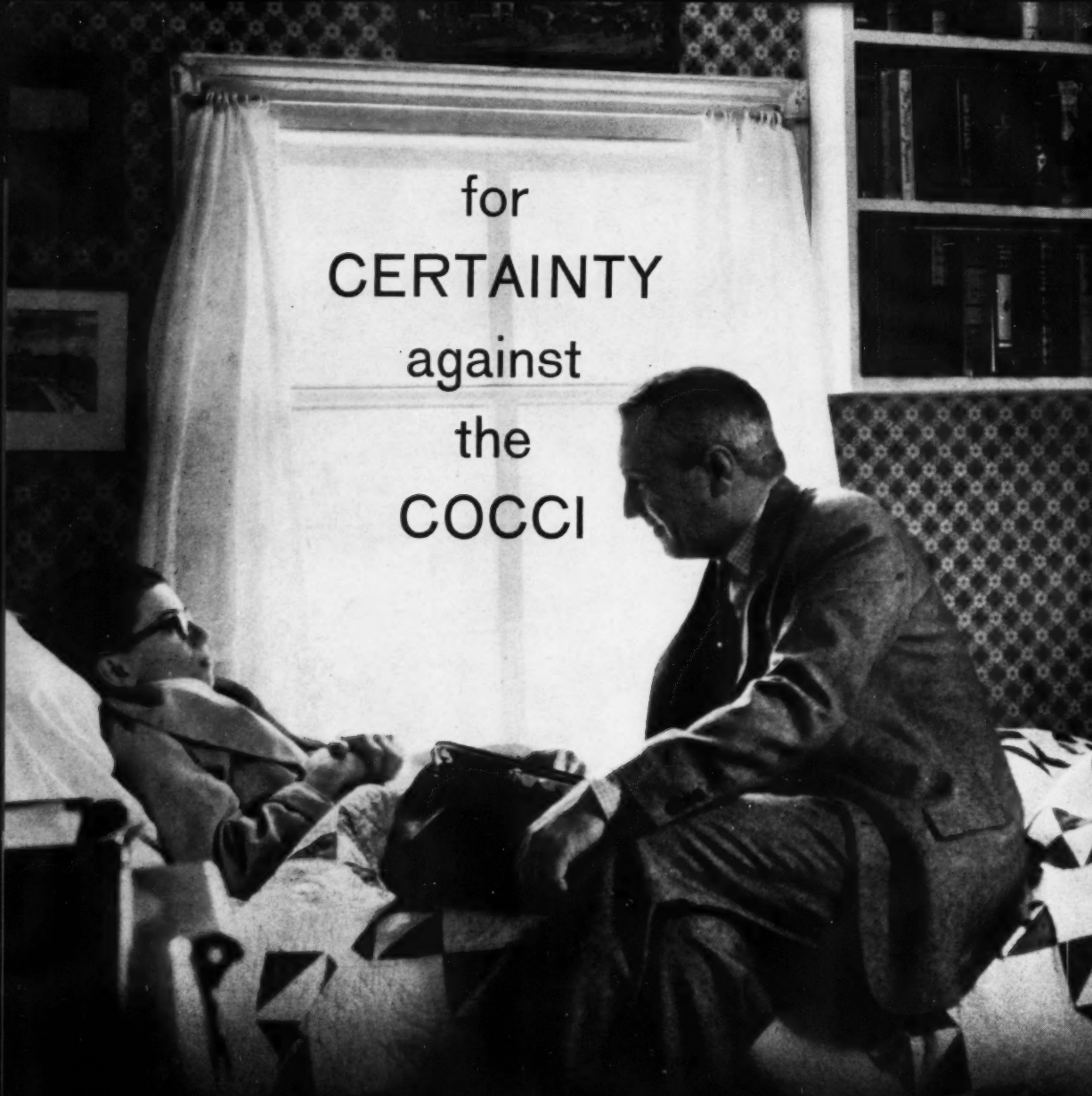
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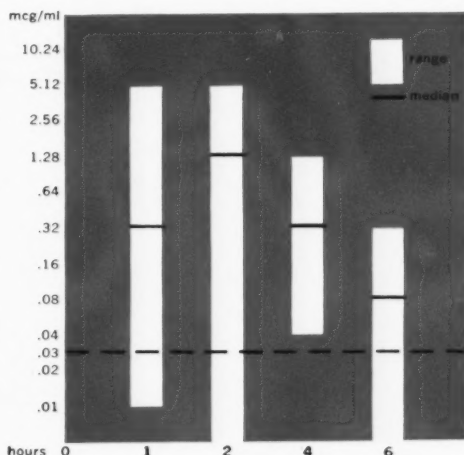
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


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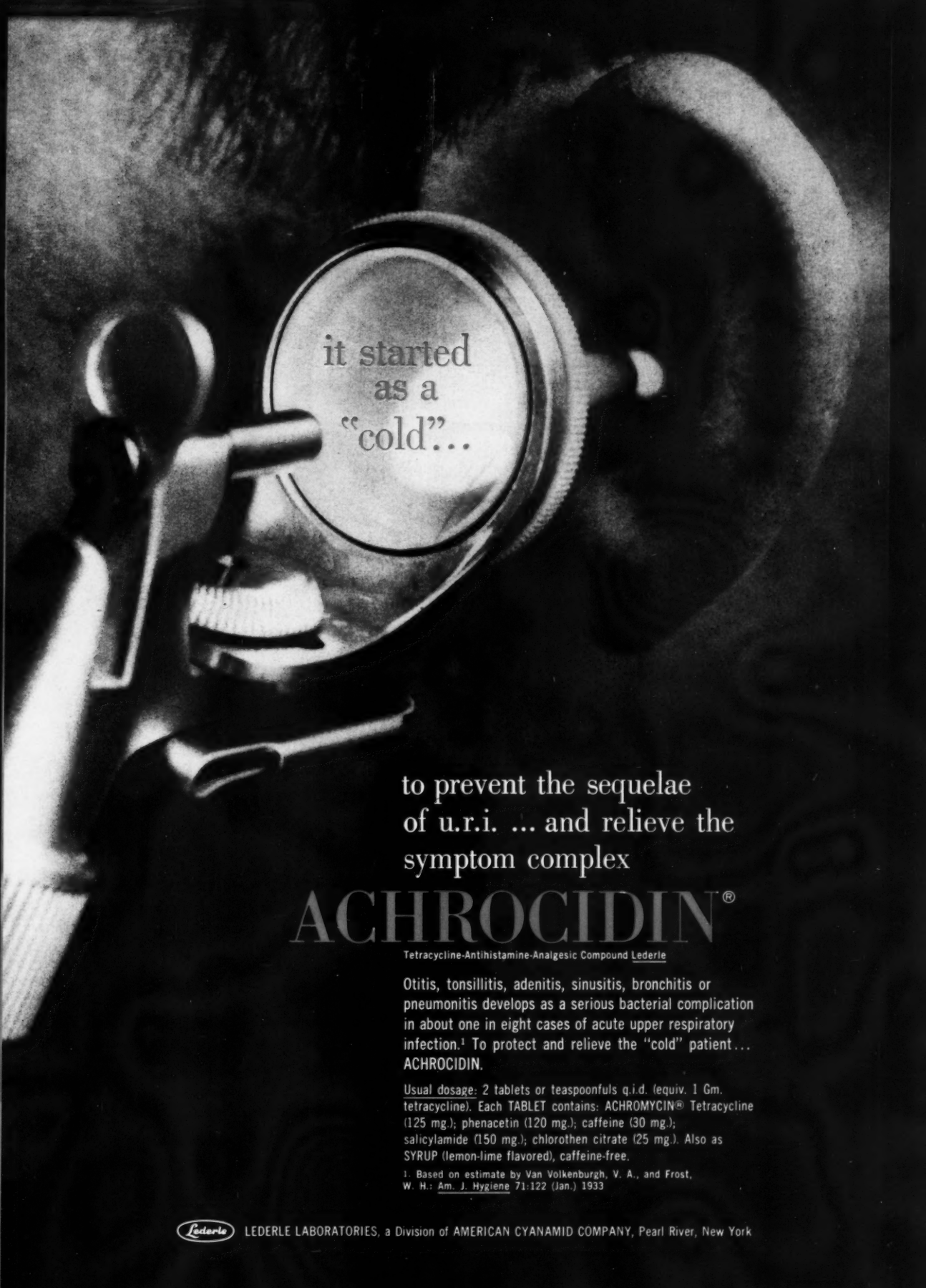
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1. Based on estimate by Van Volkenburgh, V. A., and Frost, W. H.: *Am. J. Hygiene* 71:122 (Jan.) 1933



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References: 1. Finkelstein, Murray: Journal of
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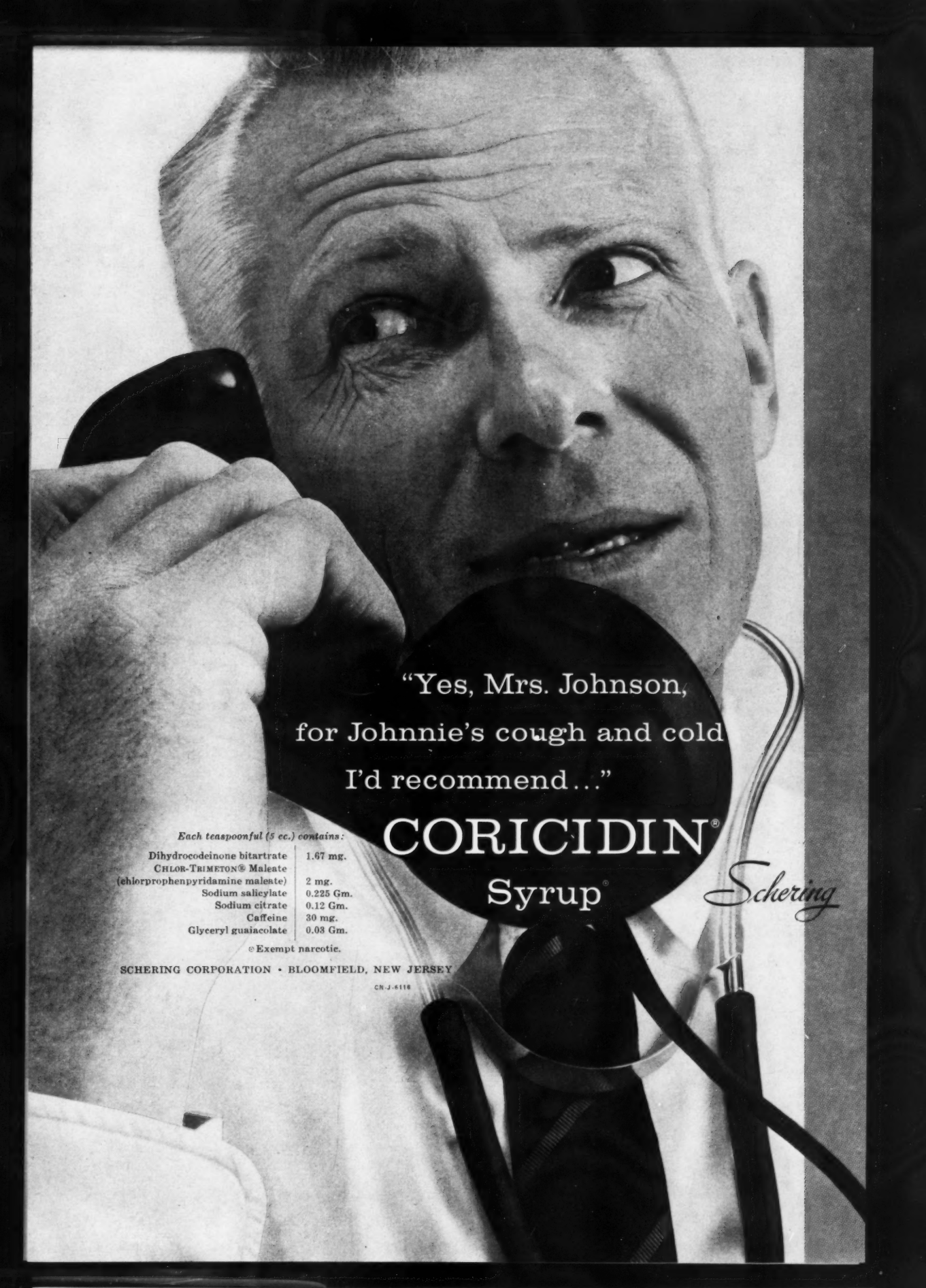
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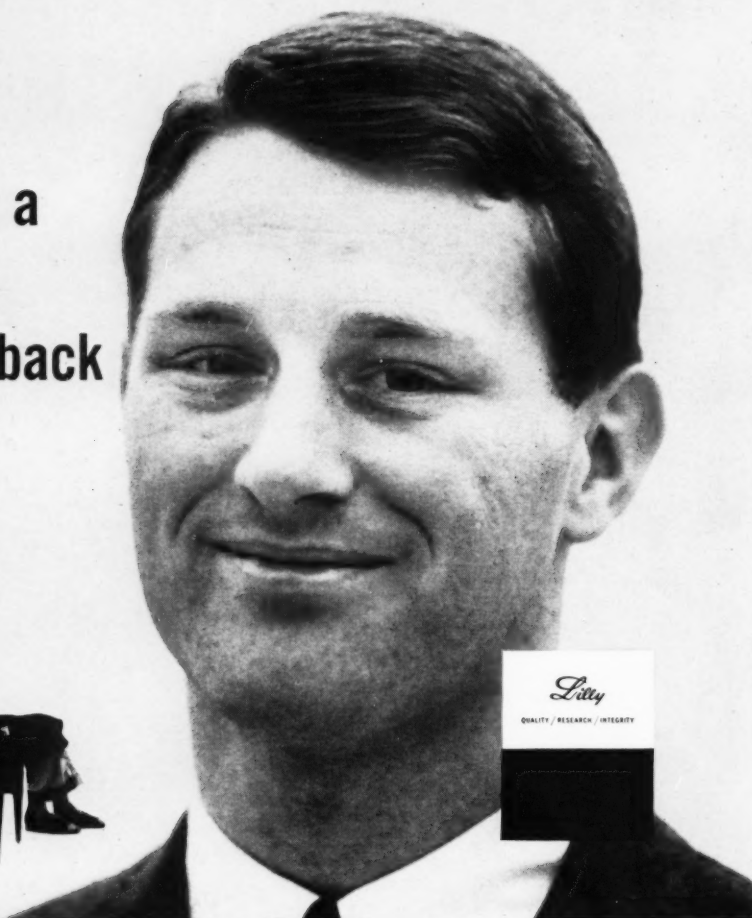
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DELAWARE STATE MEDICAL JOURNAL

*Issued Monthly Under the Supervision of the Publication Committee
Owned and Published by the Medical Society of Delaware*

VOLUME 31

FEBRUARY, 1959

NUMBER 2

RETROPERITONEAL HEMANGIOPERICYTOMA ASSOCIATED WITH HYPOGLYCEMIA AND MASCULINIZATION

JOHN W. HOWARD, M.D.* and PERK LEE DAVIS, M.D.**

Retroperitoneal or intra-thoracic fibrogenic tumors associated with hypoglycemia are one of the rare and most interesting causes of organic hypoglycemia. To the best of our knowledge, there are only 14 such tumors reported.¹⁻¹²

The following case of a retroperitoneal hemangiopericytoma associated with hypoglycemia and with masculinization is histologically similar in many respects to those previously reported.



FIGURE 1
Patient aged 16.

CASE REPORT

A 17-year-old female was in good health until the summer of 1946 when, at the age of 16, she suffered attacks of colicky, left-sided, lower abdominal pain thought to be associated with kidney stones. In November, 1946, teachers noted emotional instability and weight loss. Early in 1947 her hair, which was normally black, became drier, coarser and more abundant and showed an increased tendency to curl. (Figs. 1 & 2) In March there were episodes of flushing of the face. By May, 1947, she was no longer able to handle the work re-



FIGURE 2
Patient 1947 immediately post operative.

*Director, Department of Pathology, The Delaware Hospital, Wilmington, Delaware.
**Director, The Davis Clinic, Paoli, Pennsylvania.

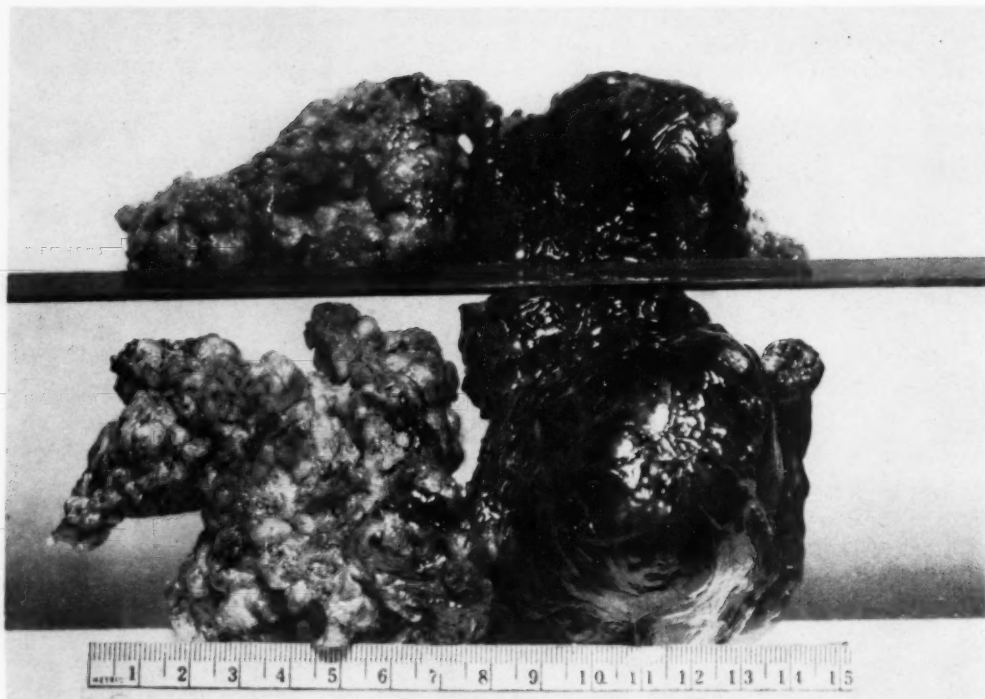


FIGURE 3
Gross specimen 1947 showing soft brainlike tissue.

quired and reported difficulty in reading and focusing her eyes. During the next two months she appeared drowsy and on eight mornings lapsed into unconsciousness. When it was found that blood sugar dropped to 30 to 40 mgm. during an attack, they were relieved with sugar or intravenous glucose. At the same time the features gradually changed and she developed an acneform dermatitis on the face, upper arms, and back.

She was admitted to the Delaware Hospital on August 6, 1947 to ascertain the cause of the hypoglycemia and at that time a pelvic mass was discovered. On admission, her coarse dry hair had normal female distribution and was greater in amount on the arms and legs. She had a dark complexion, normal breasts, and skin texture, other than face, definitely feminine. The menstrual cycle was normal. The mass noted on the left side of the pelvis was grossly the size of an orange. The blood count appeared normal. Four plus glycosuria and a fasting blood sugar of 36

mg. per cent were reported. The admission cholesterol was 245 mg., the BMR 4 plus, and the Friedman negative.

The patient was operated on August 9, and an ovoid poorly encapsulated retroperitoneal tumor mass measuring 14 x 14 x 16 cm. was found. It filled the left pelvis and appeared to arise on the anterior surface of the sacrum. (Fig. 3) The uterus, tubes, and ovaries were normal. Grossly, the tumor mass was described as numerous pieces of partly encapsulated friable tissue which was easily broken and had the consistency of brain tissue. It was uniformly yellow, chalk-white in color. Histological sections of the retroperitoneal tumor mass revealed an ill-defined, uniformly solid microscopic pattern consisting of connective tissue type of cells arranged in wavy bands and pseudo-whorls without definite design. From field to field, there were suggestions of compressed vascular spaces. (Fig. 4) Larger vessels were inconspicuous. Reticulum stains (Fig. 5) revealed a pattern compatible with hemangiopericytoma

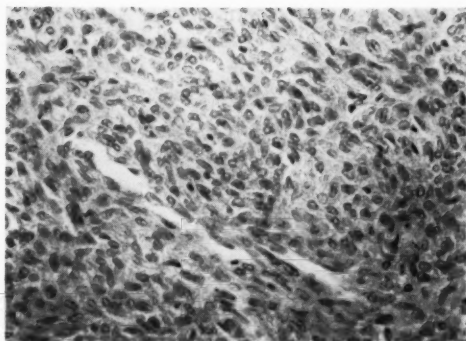


FIGURE 4
Photomicrograph of tumor showing
fibrogenic pattern.

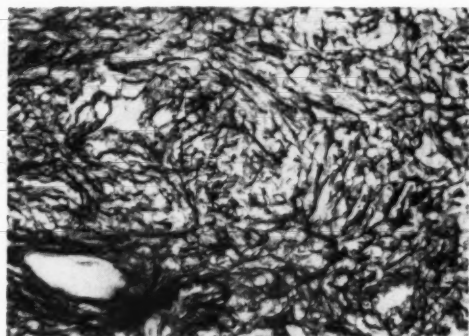


FIGURE 5
Hemanigiopericytoma. Laidlaw silver reticulum
impregnation (Foote's modification) showing
clearly defined capillary sheaths.

with many capillaries surrounded by pericytes enclosed within a reticulum sheath. Throughout there were irregular strands of collagen material associated with tumor cells. The nuclei showed few mitoses and varied in size and appearance from area to area. In some there was a preponderance of large fusiform round vesicular nuclei; in others, they were small, pyknotic, and stellate. Initial impression from responsible consultants included neurogenic sarcoma, endothelioma, sarcomatoid variant of arrhenoblastoma and malignant mesenchymal neoplasm. Subsequent review of this case by Dr. Lauren V. Ackerman and Dr. Arthur Purdy Stout suggested the diagnosis of hemangiopericytoma with which the majority now agree. No insulin assays were performed.

Post operatively, the patient recovered well. There were no further episodes of un-

consciousness and on a general diet the blood sugar did not fall below 90 mg. per cent. An insulin tolerance test revealed a fasting sugar 85 following 2.5 units of regular insulin; 30 minute sugar, 65; 60 minute, 85; 90 minute, 90 mg.; 120 minute, 95 mg. On August 28, Dr. A. E. Rakoff, Jefferson Hospital, Philadelphia, Pennsylvania, reported the urine gonadatropins as less than 6 mu. for 24 hours (diminished); 17 Ketosteroids, 2.9 mg. for 24 hours (diminished.) Urine estrogens were more than 200 mu. for 24 hours (excessive). He noted at this time that the hormone assays tended to point towards a pituitary-adrenal deficiency indicated by the low gonadotropins and the low 17 Ketosteroids. The low 17 Ketosteroids were against any masculinization tumor such as an arrhenoblastoma or an adrenal cortical tumor. In view of the high estrogens, the possibility of a granulosa cell tumor was suggested.

At the time of the patient's discharge the skin had become softened and free of lesions and the hair appeared less coarse and dry. The patient felt well and the only stigma appeared to be the thickened, kinky hair. During the next two years, the patient's condition did not change although there was some improvement in the texture of the skin and hair. She resumed her schooling until May, 1950, when a mass in the left lower abdominal quadrant was discovered. She was again admitted to the Delaware Hospital on June 5, 1950, at which time her physical condition was excellent. There was no evidence of hirsutism or previous skin or hair changes. RBC was 3 million; Hemoglobin, 10 grams. At operation a small metastatic mass of tumor tissue on the anterior abdominal wall at the site of the previous operative scar was removed together with several 5 cm. similar masses of tissue overlying the left psoas sheath. The left ovary was grossly thought to have been involved with tumor and was removed. The right ovary appeared normal. Pathological examination revealed that the ovary was normal and that the tumor was adjacent to it. The histological pattern of the tumor resembled that previously removed.

On December 12, 1951, the patient was

operated on at the Presbyterian Hospital in Philadelphia and had a right oophorectomy, a right salpingectomy, a hysterectomy and a resection of recurrent tumor in the pelvis omentum. On February 2, 1952, again at the Presbyterian Hospital, she was explored after having received nitrogen mustard. Two pieces of tissue were removed from the posterior parietal peritoneum along with iliac vessels. On both admissions, the histology appeared similar.

During the intervening time, the patient was graduated from the University of Delaware and had been teaching school (Fig. 6) She had married and in 1954 was ad-



FIGURE 6
Patient 1951 revealing normal features.

mitted to the Corona Naval Hospital in California and to the Philadelphia Naval Hospital in 1955 where additional abdominal masses of similar histological pattern were removed. The patient was followed at the Davis Clinic, Paoli, Pennsylvania, and was treated with intraperitoneal radioactive gold and intravenous TEPA together with the radiation. Anemia became a problem and on December 11, 1956, the patient returned to the Delaware Hospital for a series of transfusions to counteract the anemia, which at times was associated with a hemoglobin of 2.9 gm. The final admission was on January 18, 1957. Shortly after

admission, the patient became unresponsive although able to obey and have motor response to orders. The course was progressively downward and on January 25, 1957, the temperature rose to 104.8F and death occurred. Autopsy revealed numerous 1.0 to 10.0 cm. sarcoma nodules in the liver. There were small serosal implants on the intestine and a residual 10 cm. sarcoma nodule in the left pelvic wall at the site of the original operation. The brain showed extensive softening of the entire temporal lobe including the putamen, internal capsule and basal peduncles. The pituitary and adrenal glands were normal. Sections of the tumor were identical with those from the previous surgical specimens.

DISCUSSION

The association of hypoglycemia with tumors of apparent non-pancreatic origin has been observed with interest in recent years. Two cases associated with peritoneal pseudomyxoma¹³ and one with peritoneal mesothelioma¹⁴ have been reported. A much larger group with histological similarity has been reported and classified as fibromas, fibrosarcomas or fibrogenic tumors. To this latter group we have added another, making the current listed total of fifteen.

The present case, in addition to presenting clear-cut episodes of hypoglycemia, which did not recur after the initial operation, showed initial masculinization which also did not recur. Histologically, similar tumor recurred, but not as bulky as the original, until the terminal course. Table 1 lists the fifteen fibrogenic tumors with some recurrences associated with hypoglycemia and some not. No reported instances of associated masculinization were found.

When the fifteen fibrogenic tumors are reviewed as a group (see Table 1) they appear to have several common features. All tend to be bulky, they occur more commonly as retroperitoneal tumors although a few have been intrathoracic and each has a common spindle cell pattern that does not directly suggest pancreatic origin. How they produce hypoglycemia has resulted in many theories which have not been proved.

TABLE I
PUBLISHED CASES OF FIBROGENIC TUMORS AND HYPOGLYCEMIA

Year Reported	Author	Age Sex	Type, Location of Tumor	Size	Insulin Assay	Recurrence of Tumor and Hypoglycemia
1930	Doege (1)	50M	Fibrosarcoma mediastinum	10x6 inches 4½ lbs.		
1939	Seckel (2)	56M	Fibroma superior to right lobe of liver	Massive	Neg.	Yes
1942	Arkless (3)	45M	Rhabdomyofibroma diaphragm	2900 gm. 20x12x12 cm.		Yes
1943	Hines (4)	42M	Liposarcoma right upper quadrant	Grapefruit		Yes
1949	Staffieri (5)	25M	Spindle cell tumor, retroperitoneal	20x9x11 cm.	Neg.	
1954	Skillern (6)	68F	Neurofibrosarcoma right thorax	2440 gm. 24x18x17 cm.		
		70M	Retroperitoneal fibrosarcoma	4720 gm. 21x16x15 cm.		
1955	Howard, J. E. (7)	16F	Neurogenic fibrosarcoma region left adrenal	Grapefruit (21)	Neg.	Yes
1956	Silvis (8)	23M	Retroperitoneal fibroma	1200 gm.		
1956	Porter (9)	45F	Spindle cell tumor, retroperitoneal	20x16x13.5 cm.		
1957	Scholz (10)	47M	Perirenal fibrosarcoma	10.5x10x8 cm.		
		56M	Fibrosarcoma right lobe liver	Football	Neg.	Yes
1957	Holten (11)	41F	Retroperitoneal spindle cell sarcoma	Two fists		
1958	August (12)	82F	Intrathoracic fibrosarcoma	1370 gm. 14x14x14 cm.	Positive	
1959	Howard, J. W.	17F	Retroperitoneal hemangiopericytoma	14x14x16 cm.		

1. Stimulation of pancreatic insulin by tumor.

2. Excessive carbohydrate utilization by tumor.

3. Direct release of a hypoglycemic substance.

4. Atypical low grade islet cell tumor.

Of those listed, direct release of a hypoglycemia substance merits the greatest consideration today. Insulin-like substances (Insulinoid) in tumors has been reported.¹⁵

Several of the reported cases were assayed for insulin with negative results,^{2,5,7,10} although it is quite likely that the earlier methods used were technically not adequate. In a recently reported case by August and Hiatt¹² insulin-like activity in an intra thoracic fibrosarcoma was demonstrated. The assay utilized the rat-hemi-

diaphragm method of Vallance-Owen¹⁶ and revealed activity in the 1370 gm. tumor to be equivalent to about 600 units of insulin. This important contribution clearly indicates that a reappraisal of the metabolic nature of these fibrogenic tumors should be made. Although the technique is not suitable for the general laboratory, material can be fresh frozen and saved for assay as similar tumors appear.

The etiology of the masculinization in the present case cannot be satisfactorily explained, although initially there appeared to be some disturbance in endocrine balance and the assay nineteen days post operatively indicated a pituitary adrenal deficiency. The ovaries showed no abnormality either grossly or microscopically. Whatever the underlying cause of the early masculinization it, like the causative substance of the hypoglycemia, disappeared

after the initial operation suggesting a direct relationship with tumor tissue.

The recurrence of tumor without hypoglycemia has been noted in previous cases, and it has been suggested¹⁷ that these recurrent tumors may not be accompanied by hypoglycemia unless they become bulky. As our recurrence did not become bulky until terminally, it may be suggested that a variation in the character of the tumor can be directly related to the amount of hypoglycemic substance released. Similar theories also may explain the non-recurrence of the masculinization characteristics.

The designation of this retroperitoneal tumor as a hemangiopericytoma is the first instance in this particular group of fibrogenic tumors to be associated with hypoglycemia. In 1942 Stout and Murray¹⁸ and in 1949 Stout¹⁹ described this tumor characterized by small compressed capillaries lined by normal endothelial cells, with proliferation of spindle shaped or rounded tumor cells around these capillaries apparently arising from Zimmerman pericytes. Four of the 1949 series of 25 cases described by Stout were retroperitoneal in origin. Routine stains revealed a microscopic picture that appeared unorganized and jumbled. With the use of reticulum stains, the true nature of the tumor proliferation became evident in all cases. Later Stout²⁰ reported on thirty-two cases of hemangiopericytoma which demonstrated malignancy by aggressive growth in all and metastasis in fifteen. In this last series eight occurred in the retroperitoneum, mesentery or omentum.

The apparent histological similarity of this case with many of the published cases of fibrogenic tumors is striking. Nearly all cases presented a spindle cell pattern with varying amounts of collagen masses and an intensified vascular pattern, particularly when demonstrated by reticulum stains. Of particular interest in the case reported by August and Hiatt was the association of high insulin-like activity in areas where the tumor was more fibrous, less cellular and showed increased amounts of collagen. In contrast, the softer cellular areas from

the surface of the tumor mass were found to have 1,000 times less activity per gram.

SUMMARY

A case of retroperitoneal hemangiopericytoma associated with hypoglycemia and masculinization is presented. Initial removal of the tumor appeared to cure the hypoglycemia and masculinization. Later tumor recurrences were not associated with these changes. Fourteen similar fibrogenic tumors are briefly reviewed. The importance of modern bio-assay to aid in clarifying the relationship of this group of tumors and carbohydrate metabolism is indicated.

* * *

Acknowledgment: The assistance of Dr. Arthur Purdy Stout and Dr. Lauren V. Ackerman in reviewing this case and assisting in the histological identification has been most particularly appreciated.

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COMBINED ROENTGEN THERAPY AND HEMATOPORPHYRIN FOR SPONTANEOUS MAMMARY CARCINOMA IN MICE*

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The present article is to report on the effect of roentgen radiation and hematoporphyrin in combination on spontaneous mammary carcinoma in C3H mice. A review of this type of experiment will precede a presentation of our results.

The curability of localized neoplasms by radiotherapy is determined by the therapeutic ratio, which is a differential sensitivity between the neoplasm and the adjacent normal tissue. When the neoplasm is more sensitive, a tumor lethal dose can be given safely. In most instances the therapeutic ratio is low and a cure is difficult.

Radiosensitivity often is regarded as a fixed state or as one alterable only in the direction of increased resistance. Differences in sensitivity of various tumor species are recognized, and differences in various individuals are well known. However, the concept of varying sensitivity in the same neoplasm in the same host at different times has not been sufficiently studied. A method of favorably altering the therapeutic ratio would offer a great improvement in radiotherapy. This could be accomplished by increasing the sensitivity of the neoplasm more than that of the host, or by increasing overall resistance with a greater change in the host. A drug doubling the resistance of a tumor would still be valuable if, at the same time, it trebled the resistance of the patient.

Important advances have been made in the last three decades in the physical aspects of radiotherapy. During this time few improvements in the biological or pharmacological approach in radiotherapy have been developed. Although more physical advances will no doubt be developed, the biological and pharmacological possibilities seem to offer more promise at this time.

REVIEW

The mechanisms of the action of ionizing radiation on tissue are poorly understood, and therefore, attempts to alter these mechanisms are groping. Radiation therapy can be thought of as localized chemotherapy since it initiates cellular chemical changes. Some of the more radiosensitive components of the cell are enzymes.¹

Normal and neoplastic cells often are different in the quantity but not the quality of enzymes and metabolites present. Neoplasms often have a lower concentration of a given metabolite or enzyme than normal cells. This is the basis for antimetabolite chemotherapy. Protection of normal tissues is thought to occur on a statistical basis due to more metabolite present and more surviving.²

Ionizing radiation probably exerts its effect in much the same way, and radiation can be considered a local multi-antimetabolite. Therefore a combination of radiation and antimetabolite drugs would seem desirable. Radiation effects on tissue are mediated through cellular chemical changes, and these chemical changes should be subject to modification as are other chemical

*From the Delaware Hospital, Wilmington, Delaware, which supplied the funds and facilities for this study. We are indebted to Professor F. H. J. Figge of the University of Maryland for his valuable advice and to Baxter Laboratories for the hematoporphyrin used.

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processes. Since it has been shown that the concentrations of metabolites are different in normal and cancerous tissues, favorable alteration of the therapeutic ratio may be possible.

The comparison of chemotherapy for neoplastic and bacterial disease is interesting. Antibiotic therapy may cause death to a large percentage of infecting organisms and yet fail because of a small number which persist. The resistant organisms may succumb to a different antibiotic. Therefore it is sometimes wise to use two or three antibiotics simultaneously.

Similar reasoning applies in cancer chemotherapy. Although the neoplastic and bacterial cell populations are analogous in many ways, the reaction of their hosts is dissimilar. Ordinarily, antibiotics are potentiated by host resistance factors that are effective. Phagocytosis, antibody defense and other mechanisms come into play. Host defense factors in cancer are not understood, but they appear to be weak. Thus, chemotherapy for cancer must be thorough and effective without strong aid from the host.³

In addition to the rational approach of combining several antimetabolites and radiation, various other combinations of drugs and radiation have been studied for differing reasons. A number of studies have been carried out on purely empirical grounds. Empiricism should not be a cause for pessimism; consider the long time, successful use of many drugs, such as morphine, on this basis.

ANTIMETABOLITES

Kligerman and Shapiro⁴ have done impressive work in investigating the combination of radiation and antimetabolites. They used transplanted mammary adenocarcinoma 755 in C57 black mice and treated them with roentgen rays and several drugs. The drugs were chosen on a rational basis, each having been shown to have an antimetabolite or related effect on tumors. The drugs used were 8 azaguanine, testosterone propionate, desoxypyridoxine and 6 aminonicotinamide. Desoxypyridoxine is a vita-

min B6 antagonist, and testosterone propionate has been found to decrease the vitamin B6 concentration in tumor 755 which usually is low in this vitamin compared to normal tissue. 6-aminonicotinamide is a niacin antagonist and 8 azaguanine is a purine metabolism inhibitor.

The drugs were administered to C57 mice by multiple injections over a six day period. In the same six day period the transplanted mammary carcinomas on the thighs of the mice were given total tumor doses of 5,300 roentgens in three equal doses. Appropriate control groups were provided. Measurements were made of the tumors at the end of 25, 35 and 45 days in 5 groups embracing over 300 mice. In each group the test mice showed a much better result than the controls. Kligerman and Shapiro conclude that this type therapy is promising and their conclusion appears entirely justified.

Various other antimetabolites have been studied. Carpender and Lanier⁵ found 8 azaguanine of some value in mice in combination with radiotherapy but reported it of no benefit in humans. Lanier, Whitehead, and Gum⁶ have used aminopterin and 6-mercaptopurine with radiation in animals with some success.

Lanier, Whitehead, and Gum⁶ have used a halogenated urethane derivative to advantage in combination with roentgen irradiation of tumors in animals. In comparison with the effects in suitable control groups, the result of the urethane derivative plus radiation on two types of neoplasm in mice was encouraging. However, the best results were obtained in a group of mice receiving x-ray, oxygen and the urethane derivative.

ALKYLATING AGENTS

Roswit⁷ has used nitrogen mustard and radiation together in the palliative treatment of carcinoma of the lung. He believes that there are patients in whom the results are better than could be expected with either agent alone.

Krabbenhoft and Leucutia⁸ have used radiation and nitrogen mustard together in human patients, also. They feel that the

results show an increase in survival times and that the approach is worthwhile, especially in the undifferentiated and oat cell types of carcinoma of the lung. Their conclusions are based on an experience with 393 patients.

Lochman and Morris⁹ used radiation and radiomimetic drugs together in 20 patients with lung cancer. They did not find the combination superior to radiation alone.

Thomas³ has found the combination of nitrogen mustard and radiation of value in palliation of intractable pelvic pain caused by persistent carcinoma from the bladder, rectum, colon, and ovary. He used this treatment in 60 patients.

A small catheter is placed in the aorta via percutaneous femoral artery puncture. It is located just distal to the renal arteries by fluoroscopic control. A tourniquet is placed on each leg and 20 mg. of nitrogen mustard injected. Thereafter the patient is given 1,000 to 2,000 roentgen depth dose to the midplane of the pelvis. During the radiation the catheter is left in place and a second dose of nitrogen mustard is given after the radiation. Relief of pain is often prompt and striking.

A similar technique has been used by others in palliative treatment of carcinoma of the cervix.¹⁰

The effects of a combination of radiation therapy and TEM in animals have been studied by Lanier, Whitehead, and Gum without conclusive proof of potentiation. However, the tumor effects seem greater than with x-ray alone.

Nitrogen mustard and radiation have been used together in the treatment of lymphomas and some leukemias with probable benefit beyond that of either agent alone.

HORMONES

The Grahams^{11,12,13} have conducted extensive studies of radiosensitivity of cervical cancer. After many years' work they conclude that radiosensitivity varies with time in the same patient as well as from one patient to another. They attempted to

select by cytological means the sensitive and resistant lesions prior to therapy. They also have attempted to alter sensitivity with a number of agents. They found testosterone propionate to be the most effective agent tried. In their opinion it enhanced sensitivity to radiation to a significant degree. From their experimental work they think that the radiosensitivity of the entire patient, and not just the tumor, is the important factor in the cure of cancer. The complete destruction of a neoplasm by radiation may be due to the effect of the rays on the vascular bed of the tumor rather than on the tumor itself. If such is the case, the state of total patient sensitivity may be the important factor rather than tumor sensitivity.

Nathanson¹⁴ has used estrogens with x-ray therapy for metastatic carcinoma of the breast, and he believes that radiosensitivity is enhanced. He suggests that this may be due to an increased vascularity. This observation led others to try the same combination for advanced malignant salivary gland tumors. Eight patients were treated in this way and it was the subjective impression of the authors that more than usual sensitivity was exhibited.¹⁵

The effect of sex hormones and radiation in management of advanced breast carcinoma has been investigated also by Chu et al.¹⁶ No additive effects were found in a thorough study. The authors concluded, however, that there is no contraindication to this form of therapy and that "combined therapy is indicated in disseminated (breast cancer) disease."

Cortisone and ACTH effects on tumors treated by roentgen radiation have been studied also. Tumor bearing animals survived longer with the combination treatment than with x-ray alone, and there were fewer metastases. The authors conclude that the effects were due to hormonal modification of the radiation effect and not to a direct effect on tumor growth.¹⁷

OTHER DRUGS

Since neoplasms are often hypoxic, the effect of giving oxygen by inhalation during

roentgen therapy is a differential one in which the low oxygen concentration of the tumor is raised more than that of the normal tissue which already is at an optimal oxygen concentration. This results in an increased sensitivity in the tumor with little accompanying change in the adjacent normal tissue. Gray has studied this extensively and his work has been studied by others in both animals and humans.^{18,19,20} They agree with his conclusions.

Aureomycin has been used simultaneously with radiation in far advanced cancer. The investigators had no controls and they had only subjective impressions to report. They drew no firm conclusions but felt a number of the patients benefited from good results which could not have been expected from the radiation alone.²¹

Synkavite (sodium menadiol diphosphate) has been studied in humans by Mitchell²² as a possible radiosensitizer. Patients with various types of malignancy other than bronchogenic carcinoma were given the drug intravenously before radiation therapy and results were observed in comparison with control groups. It was concluded that the proportion of patients in the test group showing a good response was greater than in the control group. In a similar study of inoperable bronchogenic carcinoma the mean survival time from the first treatment was 9.38 months in the test group as compared with 3.89 months in the controls.

Many drugs show a protective effect against whole body radiation lethality in animals. Of these the most interesting and promising are those thought to function in protecting sulphhydryl enzymes. Cysteamine²³ and beta aminoethylisothiuronium (AET)^{24,25} are two of the best. Since tumors are sometimes poorly supplied with blood, these drugs might offer more protection to normal than neoplastic tissues. However, this has not been demonstrated and is mentioned only as a possible approach, which is the converse of various attempts to alter the therapeutic ratio by selectively increasing the response of the neoplasm.

PORPHYRINS

The phenomenon of photosensitivity caused by porphyrins has long been of medical interest. It led to studies to determine whether porphyrin-induced sensitivity extended to wavelengths in the x-ray range. Figge²⁶ studied this possibility in paramecia and concluded that porphyrins do enhance radiosensitivity in these normally resistant organisms. In other studies he has shown that porphyrins, especially hematoporphyrin, accumulate in human tissue of high mitotic index, including malignant neoplasms, some lymphatic tissues and embryonal tissue such as that found in a healing wound.²⁷

Because of the higher concentration of systemically administered hematoporphyrin in cancer, a favorable alteration of the therapeutic index is theoretically possible. Attempts to demonstrate this have not been conclusive although experiments have been conducted in mice and humans. Evaluation is difficult because of natural marked variation in sensitivity. Several observers have concluded, however, that this drug warrants further study.^{28,29,30}

MATERIALS AND METHODS

The study to be reported here was carried out with C3H mice of 18-22 grams weight. Each mouse bore a spontaneous mammary carcinoma. The mice were individually housed and were fed Purina Lab Chow and tap water at will. A two week quarantine was imposed after reception from Jackson Laboratory. The mice were immobilized and anaesthetized for irradiation by injection of sodium pentobarbital intraperitoneally. The dose was 1.25 mg. in 1 cc. of saline. Thereafter the breast tumors were irradiated with lead shields protecting the rest of the body. The irradiation factors were: KVP 100, MA 10, TSD 16 cm., filter 1 Al plus inherent, and a HVL of 2mm. Al. The calculated tumor dose was 2625 roentgen. This dose was chosen as a probable suitable dose for comparison of groups. Cures were not attempted.

Twenty mice were given 1 mg. of hematoporphyrin in 1 cc. of 1/6 M Lactate and

1.25 mg. of sodium pentobarbital in 1 cc. of physiologic saline by intraperitoneal injection. They constituted the test group. Twenty other mice were given 1 cc. of 1/6 Molar Lactate and the same anaesthetic. They were one control group.

The tumors in these two groups were comparable in size. The hematoporphyrin and lactate injections were given 24 hours before irradiation. Pentobarbital was given a few minutes before irradiation and x-ray doses were the same for the two groups.

A third smaller group was given the same porphyrin and barbital dose but no radiation.

All mice were housed and fed in the same circumstances. The entire experiment was carried out in four groups, and test and control groups were injected and irradiated within a few minutes of one another. There were 20 mice in the first group and 10 in each of three others. Measurements were made with the mice asleep. Each group was followed for 30 days after treatment and new measurements taken at the end of that time.

RESULTS

Two mice in the first group died during irradiation due to an overdose of sodium pentobarbital. One received a dose of 2.5 mg. and the other 2 mg. Thereafter each mouse received 1.25 mg. and all recovered promptly. There was a total of 20 mice in the test group.

Before therapy the tumors in this group showed a mean size of 35 cu. mm. After treatment with hematoporphyrin and x-ray the group mean measurement in 30 days was 17 cu. mm. In the control group of 20 mice receiving 1/6 Molar Lactate and x-ray the initial measurements yielded a group mean of 33 cu. mm. Thirty days later this group mean was reduced to 23 cu. mm.

In the final group of 8 mice which received hematoporphyrin but no x-ray, there was rapid growth of the tumor. In the same period of time the group mean rose from 36 to 102 cu. mm. These results are summarized in Table I.

TABLE I.

Treatment	No. of mice	Initial tumor size in mm ³ (group mean)	30 days post treatment tumor size in mm ³ (group mean)
1. 1mgm. hematoporphyrin 1.25mgm sodium pentobarbital 2625r	20	35	17
2. 1cc 1/6M Lactate 1.25mgm sodium pentobarbital 2625r	20	33	23
3. 1mgm. hematoporphyrin 1.25mgm sodium pentobarbital	8	36	102

DISCUSSION

The choice of a dose of hematoporphyrin was not entirely arbitrary. Studies done elsewhere have shown 1 mg. per mouse to be a likely choice. There is some indication that large doses such as 5 mg. per 18 or 20 gram mouse might result in an increased radioresistance.³⁰ However, some dose other than 1 mg. might be more effective. Moreover, some dose of radiation other than that used might show more pronounced effect.

The timing is probably important. Injection of the hematoporphyrin after irradiation might give better results. This has not been studied. However, Thomas has pointed out that in combined therapy the pre-irradiation use of any drug that would interfere with the oxygenation or nutrition of the tumor probably would lessen the beneficial effect of radiation therapy. It has not been shown that hematoporphyrin functions to lower oxygenation or nutritional levels. In fact, hematoporphyrin may raise the level of tissue oxygen in tumors.

The use of an anaesthetic for immobilization in this type of experiment is undesirable. It introduces an unnecessary element or variable making interpretation more difficult because it seems definite that various anaesthetics decrease radiosensitivity.²³ Despite this disadvantage it was done as a matter of convenience.

The concept of combined therapy is based on broadening the spectrum of antineoplastic activity. There is no reason to require the use of only one or two agents. The ultimate best therapy may require several agents used simultaneously because it is possible that the optimal range of ac-

tivity will come not from one agent but from a combination of several. It would be interesting to add oxygen to the combination of x-ray and hematoporphyrin. An attempt with x-ray, hematoporphyrin, oxygen and nitrogen mustard, or some other chemotherapeutic agent, should be tried. Evidence for additive effects from multiple agents used simultaneously in tumor treatment is cited previously in this article.

It should be mentioned also that additive effects have been obtained in protecting animals from whole body radiation by use of several drugs known to protect individually.³¹ The rationale of that experiment may be directly transferable to cancer therapy by radiation.

In a study of combined therapy it is difficult to determine whether the effects of the drugs are due to a change in the tumor or the host. One could make the same statement regarding the radiation. The work of the Grahams has direct bearing on this question and they suggest it is modification of the host which is most needed. There is little experimental evidence available on this aspect.

Hematoporphyrin was chosen to study because of its known effect to sensitize tissue to ultraviolet wavelengths. It deserves further study. Another drug affecting reaction to ultraviolet light is 8-methoxypsoralen.³² Volunteer prisoner subjects receiving this drug exhibited an altered skin response to Arizona sunlight. Perhaps this drug would modify sensitivity to ionizing wavelengths.

Radiation results are at best difficult to interpret because of variations in tumor dose, time of treatment, fractionation and differences in tumor species and their hosts. Addition of various drugs to the picture compounds the problems of evaluation. The use of more than one drug at a time in combination with radiation makes a difficult interpretation even more difficult. Yet the theoretical possibilities of benefit require this trial.

Radiotherapists in general are reluctant to undertake cancer chemotherapy. Many feel that this is outside their responsibility

and specialty. However, the two forms of therapy may be synergistic and may become the treatment of choice for some malignant neoplasms. If so this treatment will require a physician with special training in radiation techniques, and the logical person to manage the therapy will be the radiologist.

SUMMARY AND CONCLUSIONS

1. A review of combined roentgen ray and drug therapy for cancer is presented and discussed.
2. Results of the effect of hematoporphyrin and x-rays used together to treat spontaneous mammary carcinoma in C3H mice are presented.
3. Under the given circumstances there is probable benefit from combining this drug with x-ray therapy.
4. After a survey of other similar experiments, it is believed that this area of study is promising, and that ultimately a practical and helpful form of therapy combining radiation and antineoplastic drugs will be found.

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MOTHERS' MILK BANK AT THE DELAWARE HOSPITAL

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At a meeting of the Junior Board in the spring of 1947 Dr. M. I. Handy told of technological advances in the care of premature infants. Despite these strides, Dr. Handy cited the need for mothers' milk for those infants for whom no satisfactory formula could be found. This information struck a responsive chord with Mrs. Harry S. Trentman, whose son had benefited from the existence of the Directory for Mothers' Milk, Inc. at the Boston Lying-In Hospital. A committee of three, under Mrs. Trentman, was appointed to work with Dr. Handy in the establishment of a mothers' milk bank located at the Delaware Hospital but intended to serve the state.

From this bank, mothers' milk is available for any baby on prescription by a qualified physician. If the parents are unable to pay, milk still is provided. The Memorial Hospital, St. Francis Hospital, and Wilmington General Hospital participate with the Delaware Hospital in this program and milk is equally available to infants in these hospitals. In each hospital nurses collect excess milk from mothers and send it to the milk bank. Infants are then supplied as their needs dictate.

During the summer of 1947 a committee reviewed the Boston program and made recommendations for a start at the Delaware Hospital. The beginning was on a small scale; the milk bank made use of the hospital's milk formula laboratory, and all of the work was done by Junior Board members. The work has increased to a point where a trained worker is employed to relieve the Board members of certain duties.

Currently, two committees supervise the milk bank program. The basic working committee is made up of members of the Junior Board of the Delaware Hospital with representatives from the Junior Boards in the St. Francis, Wilmington General,

and Memorial Hospitals. The duties of this committee include distribution of special water-operated pumps, instruction of donors, collection of milk, keeping records, and processing the milk. Milk is collected from donors' homes and brought to the milk formula room where selected samples are taken for bacteria counts and water and fat content tests. It is then pooled, pasteurized, labeled, frozen, and stored.

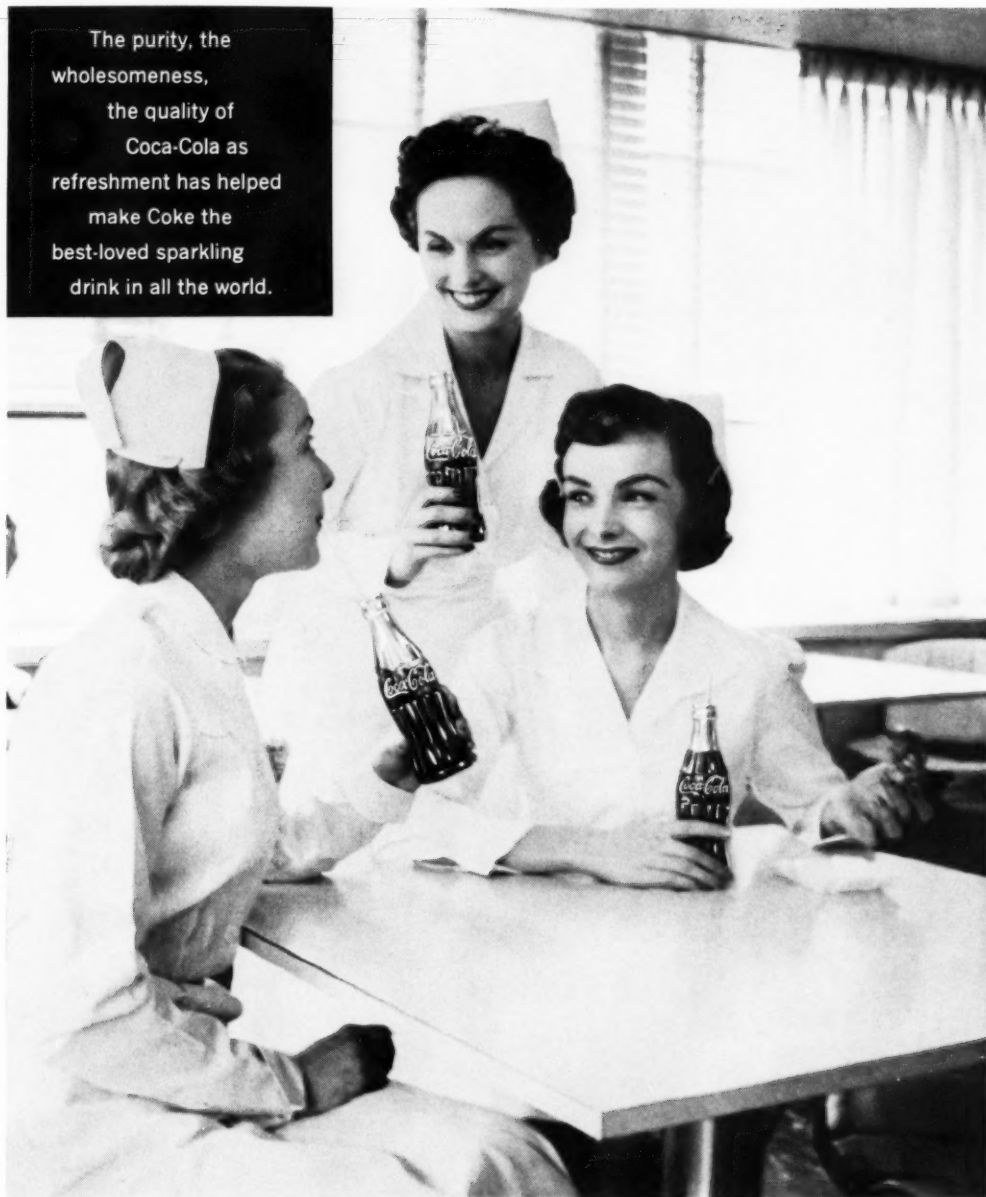
A second committee, called the Medical Advisory Committee, is made up of pediatricians and obstetricians who assist in the establishment of proper quality control and policy of a professional nature.

The milk bank has served not only patients in Delaware, but also in Massachusetts, California, and neighboring states. An infant in California required such large amounts that the milk banks of Los Angeles and San Francisco had to look eastward for an additional supply. They were referred to the Wilmington bank by the Boston Directory for Mothers' Milk which was unable to supply outside its own area at that time. The child received milk from our bank for several months.

The Boston Directory for Mothers' Milk, which furnished guidance for the establishment of the Wilmington bank through its Director, Miss Cornelia McPherson, was itself a recipient of milk. This occurred in the fall of 1957, when the supply of mothers' milk in Boston became dangerously low. Milk from the Delaware bank was used to help supply the Boston bank until a sufficient amount could be obtained in that area.

The adequate surplus of mothers' milk in a bank is dependent on the continued interest and effort of pediatricians and obstetricians. Unless mothers are encouraged to breast feed their babies, and are informed of the need for breast milk and

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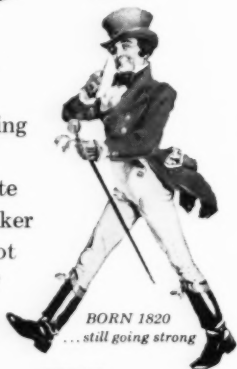
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the ease of contributing, the mothers' milk bank will fail.

There is much material in current literature, both medical and popular, concerning breast feeding. Using this for reference, the physician can usually persuade a mother to breast feed her child. A pamphlet is available for physicians' waiting rooms to aid in encouraging mothers to contribute surplus milk. In addition a letter is sent to

each new mother delivered in the participating hospitals before her discharge. Talks are given by the Chairman of the Milk Bank Committee to classes held by the Visiting Nurses' Association for expectant mothers.

Additional information concerning this program may be obtained from: Mothers' Milk Bank at the Delaware Hospital, Wilmington 99, Delaware.

EXPERIENCE WITH CHLOROTHIAZIDE (DIURIL) IN HYPERTENSIVE PATIENTS*

DAVID J. REINHARDT, III, M.D.**

Chlorothiazide (Diuril) has now been available on a prescription basis for a period of nine months. The instantaneous widespread acceptance by the medical profession at large has been little short of phenomenal. The pharmaceutical company which developed, tested, and now markets the drug has shown an increase of 100 per cent in the market value of each share of stock listed on the New York Stock Exchange. This has occurred during the past nine months and appears to be due primarily to this rather remarkable, apparently safe new diuretic agent, chlorothiazide.

The dramatic, widespread utilization of this new agent was due to several factors. First, it was said to be especially effective in treating congestive heart failure and other fluid retention states. Second, it was said to be nearly specific in the management of arterial hypertension. These two groups of patients encompass an estimated fifty to sixty million people in this country alone. The third factor was that preliminary reports indicated broad clinical safety in the use of chlorothiazide, although potential danger was suggested in long term use by its pharmacologic properties. A prior brief study, incorporating a small group of hypertensive patients, which is included in this discussion was one of these early enthusiastic reports.¹

The use of chlorothiazide has been continuous now for more than a year. The purpose of this paper is to summarize our observations on a larger group of hypertensive patients under treatment for an average period of more than six months. The

following analysis of the study group will show some of the dangers of this new drug and it is hoped, clarify the indications for the use of chlorothiazide in the broad range of the hypertensive spectrum.

METHODS AND MATERIALS

A total of 73 patients was studied. They were chosen at random and incorporated most of the etiologies of hypertensive disease. All degrees of vascular damage in the organ systems were represented. A control period of three separate visits or three separate days of blood pressure observation was carried out for each patient. The diagnosis of hypertension was made when the control diastolic pressure was consistently greater than 90 mm. of mercury. One exception is included whose blood pressure was 250/80, a patient with syphilitic aortitis, apparently involving the aorta and aortic valve.

The minimum therapeutic observation period was one month which included at least three separate visits. The maximum observation period was twelve months.

Cardiac, renal, electrolyte, metabolic, and hematologic laboratory studies were done prior to chlorothiazide and in most cases were continued periodically during the treatment period.

No restriction or cessation of other anti-hypertensive drugs was made prior to instituting chlorothiazide. The average period of observation with chlorothiazide in the 73 patients was 6.1 months.

Chlorothiazide was used in divided doses totaling 1.5 grams daily and in many instances was subsequently reduced to 0.5 Gm. as the pressure came down. An unrestricted diet was taken with only table salt limited.

* Presented at the annual meeting of the Delaware State Medical Society, October 2, 1958.

** Director of Hypertensive Clinic, Delaware Hospital, Wilmington, Delaware.
Supported in part by a grant-in-aid from the Delaware Heart Association.

In an effort to include significant alterations of both the systolic as well as the diastolic levels, the mean arterial blood pressure was used to classify the patient's response. This number is derived by adding the systolic and diastolic readings and dividing the total by two. The same figure for mean blood pressure could also be obtained by adding one half of the pulse pressure to the diastolic pressure. The mean blood pressure is also of value when working with a large study group of patients in that it is a single number and obviates the analysis of both systolic and diastolic figures.

RESULTS

The classification of results was done by averaging the mean blood pressures of each patient while receiving chlorothiazide. Diastolic grouping also was done to more clearly illustrate and confirm the results. For further simplicity, two response categories were recognized. A "good" response was considered to be either a reduction of mean pressure by 25 points, a reduction of at least 15 points to a level of 125 or below or a 50 per cent reduction of the dosage of ganglionic blocking agents with comparably good blood pressure control. All patients not fulfilling these criteria were classified as "poor" responses.

As the patients in this series represented two separate economic groups, a breakdown for this element as relating to blood pressure results was made (table 1). 76 per cent of the private patient group obtained a good response. 63 per cent of the lower economic or clinic group obtained a similar response. The differences probably are not significant statistically. There was, there-

TABLE 1

ECONOMIC DIVISION OF PATIENTS AND M B P RESPONSE			
	Total Number	Good Response	Poor Response
Private Patients	25	19 (76%)	6 (24%)
Clinic Patients	48	31 (63%)	17 (37%)
Total Patients	73 (100%)	50 (69%)	23 (31%)

fore, an overall good response of 69 per cent for the total group of 73 patients.

In an effort not to become confused by an unfamiliar term, the mean blood pressure, the adequacy of diastolic blood pressure control at or below the level of 100 mm. of mercury in both the "good" and "poor" response groups is illustrated (table 2).

TABLE 2

ADEQUACY OF CONTROL OF DIASTOLIC
BLOOD PRESSURE AT OR BELOW 100 mgm
Hg WITH CHLOROTHIAZIDE

	Total Number	Number Below 100	Percent
"Good" Response Group	50	37	74%
"Poor" Response Group	23	11	47%
Total Group	73	48	65%

In the "good" classification were 50 patients of whom 74 per cent were controlled below 100 mm. of mercury. The "poor" classification group of 23 patients had only 47 per cent below this level. The overall group showed that 65 per cent had what might be classified as adequate control with the addition of chlorothiazide. The purpose of this analysis is to indicate that chlorothiazide is not the final step, nor the answer, to blood pressure control, even when combined with other antihypertensive agents.

TABLE 3

COMPARISON OF TOTAL PATIENTS BY
DIASTOLIC GROUPING BEFORE AND
DURING CHLOROTHIAZIDE THERAPY

	Less than 100	100-125	126-140	More than 140
Before Therapy	7	46	13	7
With Therapy	48	20	4	0

Table 3 compares the previously mentioned diastolic categories, and is compared with the distribution of the average diastolic levels under treatment with this new compound. It is readily noted that a marked shift has occurred in these categories. This indicates the fact that chlorothiazide is a very significant antihypertensive agent.

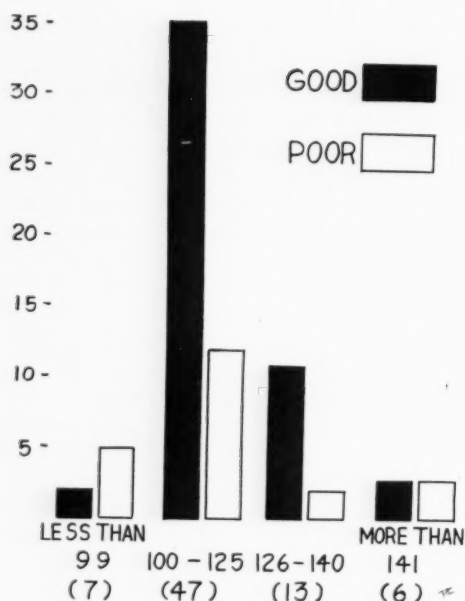


FIGURE 1
Patients responding according to pre-chlorothiazide diastolic pressure groups.

This graph (Figure 1) is a breakdown by prechlorothiazide diastolic blood pressure groups to determine if the level of the diastolic pressure is of any value in predicting whether or not chlorothiazide will be effective. The hatched bars represent the "good" response group in each category. The ordinate represents the number of patients in each bar and the abscissa shows the average control diastolic pressure groups.

Less than one third of the lowest bracket whose diastolic pressure was 99 or below achieved the "good" category. In the group between 100 and 125 more than 75 per cent obtained an adequate response. The same percentage was obtained in the more severe category of 126 to 140 mm. of mercury. The most severe group showed a 50 per cent good response. This graph suggests that those patients with only slight elevation of the diastolic pressure or those who have only a systolic hypertension will receive little and probably no benefit from chlorothiazide. The only effect one is likely to obtain may be a serious complication or, if the drug is given in a misled attempt to control a blood pressure which is not the result of arteriolarvasoconstriction but the

product of calcific vessels which have lost their elasticity, no benefit.

An attempt was made to correlate pre-treatment ranges of mean blood pressure with response to chlorothiazide (figure 2). The same trend is evident here as was seen in the diastolic pressure response. Patients with a low mean pressure respond poorly, while the percentage of good results is largest in the middle range of mean blood pressure.

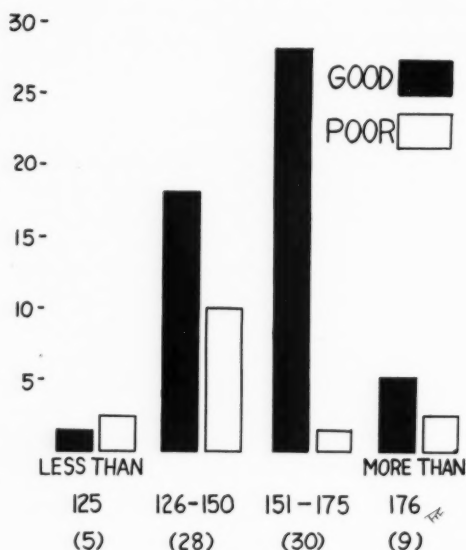


FIGURE 2
Response by mean blood pressure classification.
Good — reduction of 25 points or to 125.
Poor — all others.

TABLE 4
ETIOLOGIC BREAKDOWN OF THE
STUDY GROUP AND RESULTS

	Number	Good	Poor
1. Renal Hypertension	6	4	2
2. Moderate Essential Hypertension	25	17	8
3. Severe Essential Hypertension	11	10	1
4. Malignant Hypertension	9	6	3
5. Arteriosclerotic	18	9	9
6. Post Sympathectomy	2	2	—
7. Toxemia of Pregnancy	2	2	—
8. Neurogenic	1	1	—

An attempt was made to show response in each of the various etiologic groups (table 4). The renal hypertension classification was applied to those having either

chronic glomerular nephritis, chronic pyelonephritis, polycystic kidney disease or hydronephrosis. A positive diagnosis was obtained by kidney biopsy or intravenous urogram in each case. Four of the six in this group did well.

The moderate essential hypertensive patients were characterized by average diastolic levels between 100 and 125. Two thirds of this group had a "good" response.

The severe essential hypertensive patients did well with more than 90 per cent showing a "good" response. The importance of sodium metabolism in this type of patient is important.

Those classified as "malignant" had at some time in the past, papilledema, or showed an extremely high diastolic pressure with evidence of a rapid down hill course.

The arteriosclerotic group was so classified by a relatively low diastolic pressure a wide pulse pressure and were, in most instances, past 60 years of age. The futility of aggressive treatment is obvious in the low percentage that were benefited by chlorothiazide.

The last three groups consisting of post-sympathectomy, toxemia of pregnancy and neurogenic hypertension all showed a good response.

TABLE 5

ANALYSIS OF "POOR" RESPONSE PATIENTS

A. Essential Hypertension	8
1. Irregular visits and medication	3
2. Chlorothiazide only administered	5
B. Arteriosclerotic Hypertensive Disease	9
C. Malignant Hypertension	3
D. Renal Hypertension	2
E. Severe Essential Hypertension	1
(Probable pre-malignant)	

An interesting aspect is an analysis of those patients who did not show an adequate response to the drugs. This is done, to a degree, in the above table (table 5). The essential hypertension group had eight unsatisfactory results. Three of these were irregular in attendance and often had exhausted their supply of chlorothiazide prior to the visit. The remaining five were treated

with chlorothiazide without additional antihypertensive measures, since the hypertensive state was not considered severe enough to warrant any further additions. It must also be added that many patients classified as "poor" results in actual fact did have varying degrees of blood pressure reduction, but not enough to qualify by the above mentioned standards.

The nine patients responding poorly in the arteriosclerotic hypertension group are remarkable only in that the "poor" results were not greater in number. Hypothetically, one would expect 100 per cent to be failures. The frequently seen arterial pressure elevation that occurs as a compensatory feature in early and frank congestive failure may contribute toward the misleading impression given by the 50 per cent who had a significant reduction in pressure with the addition of chlorothiazide.

The three failures in the malignant group also are understandable. This classification of hypertension is ill-defined and is clinically applied to any patient with a rapid progressive course which may at one time demonstrate the reversible entity of papilledema. Pathologically, it is the vascular lesion of the kidney described as arteriolonecrosis. Bechgaard² in his exhaustive study of 1,000 hypertensive patients followed for a period of 16 to 22 years, found only 13 who developed the "malignant" stage of hypertensive disease and these occurred during the first ten years of the study. This work would suggest that malignant hypertension is of a different etiology as compared to essential or severe essential hypertension.

In the above listing of nine malignant hypertensive patients who were treated in the study group, two had had sympathectomy. The resulting total of seven patients without sympathectomy showed four with adequate response and three who did not respond. Still, analysis of those classified as a "good" response reveals that the diastolic pressure was improved, but still not adequate, and did not achieve the generally accepted level for good control of 100 mm. of mercury or less. This would suggest that one or more types of pressor response was

active, and that sodium metabolism plays a rather insignificant part in the overall pathogenesis of the malignant picture.

The failure of control in one third of the renal hypertension group would point toward a humoral basis for this type of disease with sodium playing a variable and probably minor role.

The single failure in the severe essential group of 11 patients was probably due to the fact that the patient was in the malignant category but progression had been retarded by early drug therapy using older agents.

TABLE 6
RESPONSE BY TOTAL MONTHS
OF THERAPY

	1-3 months	4-6 months	7-9 months	10-12 months
"Good" Response (50 Patients)	7 (14%)	19 (38%)	8 (16%)	16 (32%)
"Poor" Response (23 Patients)	8 (35%)	6 (26%)	4 (17%)	5 (22%)

One had the clinical impression that the patients' blood pressure would progressively improve as month after month of chlorothiazide administration continued. In an effort to substantiate or deny this impression (table 6), the "good" and "poor" groups were separated as to the total time of treatment in three month periods. The first three month period contained 14 per cent of the "good" response group as compared to 35 per cent of the "poor" group. A further breakdown to the two month level showed a ratio of "good" to "poor" response group of 22 per cent to 81 per cent. This further suggests increasingly good response with prolonged administration, and that the development of drug fastness with chlorothiazide does not occur, at least in the twelve month period from which these observations were taken.

As was previously mentioned, additional antihypertensive drugs seemed to increase the blood pressure response (figure 3). This graph shows the three groups of patient results when broken down into categories of types of drug therapy programs. It must be remembered in evaluating this graph that with each additional drug a more

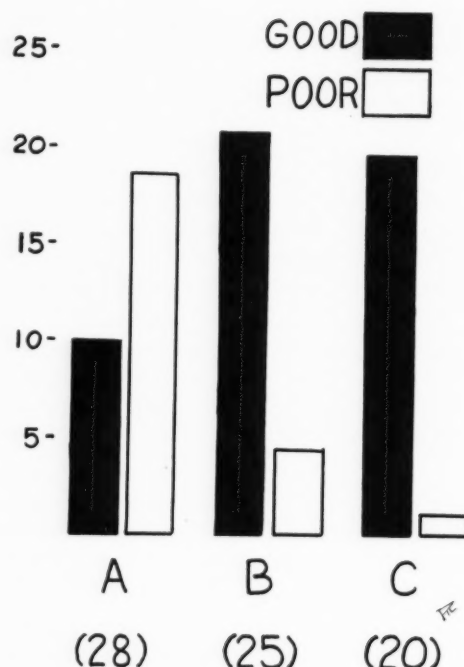


FIGURE 3
Response of mean blood pressure with and without other anti-hypertensive drugs.
A—Chlorothiazide alone.
B—Chlorothiazide and reserpine.
C—Chlorothiazide and reserpine and/or hydrolozine and/or mecamlomine.

severe grade of hypertension was present. In all instances chlorothiazide was added to the previously established program with the exception of those receiving chlorothiazide only. Most of the patients were in the diastolic range of 90 to 125 and were also newly discovered, thus they received no prior treatment. Because of the difference of degree of hypertensive severity between the groups, the percentages of response cannot be accurately compared. This applies specifically to the last group where three or four agents were needed. However, the first two groups are more similar. Chlorothiazide alone produced a "good" response in only one third of the patients.

However, 21 of 25 patients were classified as "good" when reserpine was added.

One would expect to find an excellent blood pressure response in those patients with congestive heart failure. Twenty-nine patients, or one third of the group were

TABLE 7

MEAN BLOOD PRESSURE RESPONSE OF PATIENTS UNDER DIGITALIS THERAPY

Good Response	19
Poor Response	10
Total Patients	29

under treatment with digitalis. The "good" response criterion was fulfilled in two thirds of this group. This figure was much lower than anticipated. A recapitulation suggested that this group contained many arteriosclerotics and also many patients with terminal vascular degeneration, from which a marked pressure reduction could not be expected and might not be desired. It must be noted that nearly every patient in this category had a reduction in severity of the heart failure.

TABLE 8

MEAN BLOOD PRESSURE RESPONSE OF PATIENTS WITH RENAL IMPAIRMENT

Good Response	9
Poor Response	6
Total Patients	15

Table 8 shows an attempt to evaluate the effect of chlorothiazide on hypertension when renal impairment was a factor. Again, the same percentage of patients showed improvement. This indicates that varying degrees of renal failure are not alone a contraindication to blood pressure control with chlorothiazide.

TABLE 9

BEHAVIOR OF BUN WHEN RENAL IMPAIRMENT IS A FACTOR (15 PATIENTS)

BUN not changed in 8
BUN lowered in 2
BUN increased in 5

While considering kidney impairment, it was necessary to determine if the chlorothiazide would act in a toxic manner and accelerate the uremic process. Fifteen patients with urea elevation were studied and the results show only the usual downhill progression one would normally find over a period of six months.

TABLE 10

SIDE EFFECTS UNDER THERAPY

A. Incidences of Side Effects	
Private Patients	16 (64%)
Clinic Patients	8 (16%)
B. Type of Side Effects	
Constipation	7
Chronic fatigue	6
Improvement of nocturia	4
Dizziness	4
Muscle aches	3
Epigastric distress	2
Nausea	2
Mental depression	1
Diarrhea	1
Anorexia	1
Pruritis	1

In any pharmacologic evaluation, the incidence and type of side effect from the drug is important. Because of the differences in good management, intellectual capacity and physician-psycho-therapeutic element the economic division was applied to the whole group (table 10). It was evident that private patients were more sensitive, observant and probably more imaginable than the indigent clinic group. The differences of incidence of side effects of 64 per cent for the private group, compared to 16 per cent for the clinic group is striking, and indicates an important factor to be considered when evaluating a drug for the clinic-type patient. It also is indicative of the private patients' excessive introspection which must, at times, lead to imaginary symptoms. This also would reduce the value of the results from an objective standpoint. The economic breakdown only proves the value of having a combined evaluation in both groups to understand the true incidence of side effects.

The types of side effects were variable and, with the exception of the first four items listed, probably are not related to chlorothiazide. The common complaint of constipation could be due to a relative dehydration with an increased reabsorption of water from the bowel and hence a hard stool. The chronic fatigue of which six patients complained was suspected of being due either to electrolyte imbalance or sudden reduction of the blood pressure. However, the electrolytes in these patients were

found to be normal. It also was noted that there was no sudden drop of pressure in this group. Many other patients who had a sudden drop of pressure failed to complain of this sensation. One wonders about the effect of chlorothiazide on the metabolic balance of some of the lesser known trace elements for which accurate measurements are not clinically available.

The reduction of nocturia was a beneficial side effect which was not predicted at the start of the study. It occurred in patients with prostatic hypertrophy who were slightly obstructed at the bladder neck. The daily mild diuresis caused by morning administration of chlorothiazide apparently produced a mild nocturnal dehydration resulting in a reduction of urine excretion. The dizziness noted in four patients was actually a postural hypotension associated with change of position and did not require cessation of therapy.

TABLE 11

COMPLICATIONS UNDER THERAPY		
Hyperuricemia	(8 of 40)	20%
BUN elevation (Previously normal BUN)	(3 of 61)	5%
"Low Salt Syndrome"	(Whole group)	3%
Hyponatremia	(2 of 50)	4%
Hypokalemia	(1 of 55)	2%
Digitalis Intoxication	(3 of 29)	10%

Metabolic alterations and relatively more serious developments were considered under the heading of complications. The blood uric acid was elevated to abnormal levels in eight of forty patients tested. No acute gouty attacks developed during this period. Only one patient had a previous diagnosis of gout. The uric acid abnormality has been postulated by others³ to be the result of chlorothiazide acting on the lower tubule where the excretion of uric acid takes place.

The development of elevation of the blood urea nitrogen in three of sixty-one patients was duly recorded but was not seriously considered as a complication. A group of hypertensive patients of this size could normally be expected to show this change over a six month period.

Three patients developed a clinical low salt syndrome. Hyponatremia was proved in two patients of fifty who had serial blood

electrolyte studies done. In one of fifty-five patients hypokalemia was demonstrated. However, digitalis intoxication developed in 10 per cent and this may well represent either an intracellular reduction of potassium or possibly an alteration of the ratio of potassium to sodium at the cellular level.

TABLE 12

DEATHS UNDER THERAPY		
Total Number.....4 Patients		
Diagnoses:	Chlorothiazide a factor	
A. Coronary Thrombosis	1	Possibly
B. Bronchogenic Carcinoma	1	No
C. Uremia (Chronic Nephritis)	1	Accelerating Factor
D. Low Salt Syndrome	1	Yes

The last analysis brings into sharp relief the greatest danger associated with a new potent pharmacologic agent.

In the group of 73 patients four died. In two of these it was felt that chlorothiazide was a contributory or accelerating factor and in one it was felt to have been the causative factor. The fourth was due to a bronchogenic carcinoma and therefore not implicated.

The first patient was a 52-year-old male who had a rather marked postural hypotension while under treatment with reserpine and chlorothiazide. His control blood pressure averaged 220/140 and moderate left ventricular hypertrophy was present. There was no suggestion of coronary disease by electrocardiogram or history. His treatment blood pressure showed a progressive reduction to the level of 110/70 at the end of six months. His wife related that he suddenly arose on the day of death to the standing position. He was immediately unsteady and complained of dyspnea which was followed by a crushing substernal pain not relieved by lying down and which was followed in 30 minutes by sudden death. The autopsy showed a fresh coronary thrombosis without infarction. It seemed reasonable to believe that the antihypertensive program was a strong contributory factor to death.

The second patient had uremia of a moderate degree and severe hypertension. The

blood potassium level was 7.0 meq. and the sodium was 133 meq. when chlorothiazide was initiated. He was placed on a full salt diet with 4 grams of sodium bicarbonate added. Chlorothiazide was started at a dose of 2 grams daily in an effort to reduce the hyperkalemia while supplying adequate exogenous sodium to prevent further depletion. On the seventh day vomiting developed, with intense weakness and muscle aching. At this time the sodium had dropped to 110 meq. and the potassium was even further elevated to 8.0 meq. The electrocardiogram showed changes suggestive of hypermagnesemia. Death followed shortly. Post mortem examination showed the small granular kidneys of chronic nephritis. Chlorothiazide triggered the rapid demise of this otherwise chronically ill but relatively stable patient who undoubtedly had a salt losing type of nephritis.

The third was a severe hypertensive patient under chlorothiazide treatment for six months. Moderate renal impairment was evident by borderline urea levels. Under stress, such as mild systemic viral infection, the urea would become elevated. Therapy included reserpine, hydralazine and mecamylamine. Following a brief period of several days of hot weather the patient complained of weakness, nausea, and constipation. The blocking agent was discontinued and a laxative given. The following day the patient was acutely ill with weakness, diarrhea, vomiting and had developed auricular fibrillation. The electrocardiogram failed to demonstrate any new myocardial or electrolyte abnormalities. It was unfortunately not possible to obtain blood sodium and potassium determinations. Other laboratory studies revealed the CO_2 to be 19 meq., BUN 96 mgs. per cent, Chloride 85.6 meq. with an alkaline urine. Saline was started intravenously but the patient died on the third day of illness shortly after the laboratory studies were obtained and before effective therapy for the suspected severe hyponatremia had been carried out. Post mortem examination was not granted. It was surmised that an acute low salt syndrome was produced by a combination of minimal renal function impairment, hot weather and chlorothia-

zide which resulted in sudden death. Renal function in the previous two years was identical with that just prior to the onset of the sudden terminal illness. The only factor which was different was chlorothiazide. The observers were in agreement that the terminal acute illness was probably precipitated by chlorothiazide.

After careful analysis of these three deaths it is concluded that chlorothiazide may be a factor in causing one death in as few as every 25 hypertensive patients under long term therapy.

DISCUSSION

The diagnosis of essential hypertension is still, after many years of intensive investigation, a common category which probably includes many different physiologic abnormalities characterized by increased peripheral arteriolar resistance. The most common abnormality is seen in sodium metabolism and it is in this type of patient that the saluretic activity of chlorothiazide is most beneficial. Other hypertensive states caused predominantly by humoral agents of the kidney or the central nervous system would not be expected to respond, as any change of sodium metabolism in these instances would be due to a prolonged hypertension. Consequently, sodium depletion by diet, resins or chlorothiazide would result in little if any improvement. I believe that the so-called malignant hypertension is of a different etiology than is essential hypertension with its demonstrated sodium metabolic fault.

It would then appear that a lack of improvement in a severe hypertensive state following therapy with chlorothiazide could be considered a diagnostic test and stimulate the therapist to a more extensive evaluation for some of the less frequent causes of hypertension.

In the earlier report of a small segment of this patient group the use of chlorothiazide was felt to be free of danger. The more extensive experience herein reported has produced a sobering realization that chlorothiazide is a potent chemical compound which can be deadly, especially in

patients with vascular damage from years of uncontrolled hypertension.

SUMMARY

1. 69 per cent of the general hypertensive population had a significant reduction of blood pressure when chlorothiazide was added to the present program.
2. No significant response difference is noted between the upper and lower economic group.
3. When the diastolic pressure is below 100 mm. of mercury prior to treatment it is unlikely that chlorothiazide will be of any benefit.
4. Systolic hypertension in an elderly individual should not be treated with chlorothiazide.
5. Renal and malignant hypertension should be treated with chlorothiazide although sodium is probably of minor importance in hypertension of these etiologies.
6. It appears that therapy with chlorothiazide should not be discontinued as ineffective in less than four to six months because of the apparent increasing effect with prolonged usage.
7. Chlorothiazide used alone is seldom effective.
8. Chlorothiazide and reserpine appear to be an excellent combination for moderately severe hypertensive patients.
9. No evidence of drug fastness with long term therapy has been noted.
10. Patients under therapy with digitalis were found to respond as well as the overall hypertensive group.
11. Renal failure does not contraindicate the use of chlorothiazide; however, close observation is necessary as complications are more likely to develop in this group.
12. Hot weather increases the likelihood of electrolyte complications.
13. Digitalis intoxication developed in 10 per cent of treated patients.
14. Three deaths occurred in which chlorothiazide was suspect.

* * *

Appreciation is expressed to the Merck, Sharp and Dohme Co. for supplies of chlorothiazide as Diuril and mecamlamine as Inversine; to the Ciba Pharmaceutical Co. for supplies of hydralazine as Apresoline and reserpine as Serpasil.

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1. Reinhardt, D. J.: The impact of chlorothiazide on therapy in arterial hypertension, *Delaware M. J.* 30:1, 1958.
2. Bechgaard, P.: One thousand hypertonics followed for sixteen to twenty-two years, Abstract 3rd Inter. Cong. Int. Med., 17, 1954.
3. Laragh, J. H., Heinemann, H. D., and Dmartini, F. E.: Effect of chlorothiazide on electrolyte transport in man, *J.A.M.A.* 166:145, 1958.

+ Editorial +

This issue of The Journal contains several excellent articles that undoubtedly would have been published in a larger journal with national circulation had their authors so desired. We are pleased that it was decided to publish them in the authors' state journal. They will be widely read; at least one will be abstracted in the national journals. It is a good thing for The Journal to have articles of this calibre.

On the other hand it is hoped that these articles will not deter prospective young authors from submitting their material for publication due to a feeling of inferiority.

We have stated in the past that this is your journal; that the case report is a desirable subject for publication; and that a state journal is an excellent medium through which young physician-authors may gain experience. After almost three years in the job, your editor has some ideas on these subjects:

There is a wealth of clinical material in the state of Delaware. There are four general hospitals in Wilmington, four downstate, and four hospitals throughout the state limited to specific types of patients. In looking over recent issues of The Journal, it is obvious that this great source of material has barely been touched.

Some of the hospitals mentioned above have residency training programs. Physicians in training are preparing themselves for the practice of a medical specialty and it is desirable that the specialist make his views known to his colleagues by writing. The state journal is an excellent field upon which to train medical writers. Many of our

younger physicians refrain from writing case reports because of the belief that to do so would entail a detailed search of the literature, a time consuming procedure. This is not true. Many a good case has been ruined in its presentation by reason of too much extraneous material. A busy physician will not read what fifty previous authors said about a subject but he will read with interest and benefit a brief report that tells (1) what the patient had wrong with him, (2) how his condition differed from that seen in others, (3) the treatment used, (4) the course of the case, and (5) one good reference containing further references for those interested. Such an article is mutually beneficial to author and reader.

Many young physicians believe that writing is easy and that practice is unnecessary. They believe that as long as they keep up in their reading, they can merely sit down and write a finished paper in one draft. Many do just that, but papers so written rarely reach the typesetter. Good writing is hard and tedious work and consists of writing, rewriting, and rewriting. The state journal is equipped to give these young authors help; help for which they would be charged dollars and cents elsewhere. If their subject matter has any merit whatsoever, the paper is carefully reviewed by a professional copy rewriter who frequently corrects grammar, sometimes changes style, but never changes the meaning. The opportunity to see these manuscripts before and after revision is valuable training. From such training comes experience.

This is your journal. Support it and it will help you.

THE AUXILIARY'S CHALLENGE TO PROVIDE NURSES FOR A CHANGING WORLD AND A GROWING NATION

It would be as easy to tell of the exact beginning of time as to state the exact beginning of nursing. In pre-historic times, nursing was carried on in a crude form as cavewomen cared for their children and nursed the wounds of their men injured in battles and hunting expeditions.

As far back as 6,000 B.C., we read in the earliest written records of ancient civilization of customs of caring for the sick—some helpful, some harmful, some methods based on magic and superstition, and others still practiced in some form today.

In the time of Hippocrates groups of individuals were working together at nursing. These were religious groups devoting their lives to charity. During the dark ages when religious orders were in constant disagreement, nursing fell into disrepute. Only women of the worst sort would brave the homes and prisons to care for the helpless and the sick. It is from this era that Charles Dickens created "Sairy Gamp", who to this day stands for someone slovenly, always drunk, and completely immoral.

During the 1700's, groups of women known as Sisters of Charity, deaconesses, etc. were taught enough by physicians to enable them to give at least a minimum of care to patients.

In 1820, with the birth of Florence Nightingale, a light dawned on the history of nursing. She came from a wealthy English family and her work in the horror and bloodshed of the Crimean war is a story every history student knows. It was she who paved the way for women of the upper classes to enter this field, and, when she founded the first school of nursing at St. Thomas Hospital in London in 1860, she also founded the model for all training schools to follow.

After 1860, nursing as a profession grew and spread like a giant mushroom as more and more schools were founded. Nurses were now given the best of training as well as recognition of their place in society. During World Wars I and II, nurses added more laurels to their profession with their accomplishments on the battlefields of the world.

Times have changed so fast that the nursing profession is still struggling to catch up. Due to the shortage of nurses, we are grappling with one of the fundamental health problems of our time, and it is important that we plan activities and services both immediate and long term. There will continue to be a growing demand for nursing service over the next few decades. Experiences of the past half century have established trends which make such a demand inevitable.

In the years ahead, the population will increase by an unprecedented measure. More people will live to an older age, heirs to the degenerative diseases of longevity. Medical practice will broaden in scope with more precise methods of diagnosis and treatment. Public health and community service will expand. Society will demand more of the benefits of a growing knowledge of health and medical science as people become increasingly aware of these benefits.

With such prospects, only ordinary vision is required to realize that more nursing personnel will be needed for the myriad of other services expected of the nurse. Nursing education, as is true of education in many other professions, must prepare an adequate number of highly skilled practitioners so that nursing service may utilize a large and growing number of lesser prepared personnel. Only thus, can nursing assure to society the services society will demand of nursing.

Ahead, we can look for a healthy student potential. The war babies who skyrocketed the national birthrate are reaching college age. To nursing, this augments an expanding student enrollment. The post-war student deluge has reached the secondary schools. To keep pace with the growing nation and the rapid strides of medicine, nursing school applicants will have to be doubled by 1970 and now is the time to provide the potential teaching and supervisory staffs for these coming years.

In 1950 the Woman's Auxiliary became active in the Nurse Recruitment program. This was conceived fundamentally as a means of guiding young people to become deeply enough involved in the prospects for service in the profession that they would choose it as a career. We are still greatly concerned with the growth of the nursing profession, a growth that can be nurtured only through a most careful screening of the persons who will find professional service one of the chief ingredients of a satisfying life.

WHAT WE HAVE DONE

Since 1950, the Auxiliary has—

1. granted twenty-eight nursing scholarships to students entering training schools in Delaware.
2. sponsored an annual bridge party and fashion show to provide the funds for these nursing scholarships.
3. screened applicants for the Rotary Club of Wilmington and have selected forty-four successful candidates to enter training schools in the city of Wilmington. This is a remarkable record of achievement, and we publicly express our gratitude to the Rotarians for their support in this community service.
4. screened an applicant for the Zeta Chapter of the Beta Sigma Phi Sorority.
5. worked with the American Nurses Association in establishing Future Nurses Clubs in the high schools of Delaware.
6. provided refreshments for senior high school students who have attended pro-

grams on "Nursing as a Career".

7. provided each of the high schools in the state with information regarding our scholarship program and material for their library shelves on "Nursing as a Career".
8. manned the "Career Day" booth at the Harrington fair and provided bus transportation for attending students.
9. supplied information to applicants as to where they can apply for other sources of financial help or loans to pursue the career of nursing.

These are but a few of the projects undertaken by the Auxiliary to promote the recruitment of nurses.

We hope our program is still in the infancy stage, because the supply is still very short of the demand. Scholarship aid is recommended to encourage those students who could not otherwise afford a nursing education, but who show indication of succeeding in a career in nursing. Scholarships for nurses can help provide the people of Delaware with sufficient high quality nursing service to maintain and improve community health. Everyone who uses nursing service, whether directly or indirectly, has a stake in helping to assure more and better nursing care.

HOW YOU CAN HELP

To you who are doctors.

You often have an opportunity to counsel patients or the sons and daughters of patients about their future careers, and many people turn to you for advice about entering nursing. Do you have up-to-date information about the opportunities for nurses, the types of educational programs, and other important facts at hand so that you can give informed guidance? Nursing career materials in your patients' waiting room are an effective aid to recruitment.

Some of our doctors have already established a yearly scholarship in the hospital of their choice. Would you care to do likewise? The cost of a nursing scholarship is between one hundred and fifty dollars and

three hundred dollars for the three year course depending on the individual hospital.

To you who are graduate nurses.

Remember that you do more than anyone else to influence the public's attitude toward nursing. A satisfied nurse who is vocal about her profession is the most efficient recruiter nursing can have. Keep up with what is happening in nursing so that you always know its selling points as a career.

To all Auxiliary Members.

Support our annual bridge party either

by attendance or a contribution. The proceeds from this affair are solely for the Nurses Scholarship fund. Remember the date this year is TUESDAY, APRIL 21, at the DU PONT COUNTRY CLUB.

Let us do all that we can to help those who accept the challenge of human service and have the assurance that in no other line of endeavor are the rewards so high and the satisfaction so enduring.

Kathleen E. Aikins (Mrs. James P.)
Chairman: Paramedical Careers
Recruitment Committee
Woman's Auxiliary to the
Medical Society of Delaware.

MAJOR MEDICAL MEETINGS IN DELAWARE

Standing Schedule

Beebe Hospital	General Staff	2nd Friday	Monthly
Delaware Hospital	General Staff	2nd Tuesday	Feb., May, Sept., Dec.
Kent General Hospital	General Staff	3rd Tuesday	Monthly
Memorial Hospital (Wilmington)	General Staff	2nd Tuesday	Jan., March, June, Oct.
Milford Memorial Hospital	General Staff	2nd and last Tuesdays	Monthly
Nanticoke Memorial Hospital	General Staff	1st Thursday	Monthly
St. Francis Hospital	General Staff	4th Tuesday	March, May, Oct.
		1st Tuesday	December
Wilmington General Hospital	General Staff	4th Tuesday	Jan., April, Sept., Nov.

Kent County Medical Society	Monthly Meeting	3rd Tuesday	September - June
New Castle County Medical Society	Monthly Meeting	3rd Tuesday	September - June
Sussex County Medical Society	Monthly Meeting	2nd Thursday	September - June

Delaware Academy of General Practice	Monthly Meeting	1st Tuesday	September - June
Delaware Pathology Society	Weekly Meeting	Each Friday	

Special Schedule

Medical Society of Delaware	Medico-Legal Symposium	A. I. du Pont Institute	February 22, 1959
Medical Society of Delaware	Seminar on Obstetrics	Milford Memorial Hospital	March 25, 1959
Medical Society of Delaware	Annual Meeting	Academy of Medicine	October 14-15, 1959
American Medical Association	Annual Meeting	Atlantic City, N. J.	June 8-12, 1959
Delaware Academy of General Practice	Symposium on Cancer Detection and Treatment	A. I. du Pont Institute	April 25, 1959
Delaware Academy of General Practice	Annual Meeting	Academy of Medicine	December 5, 1959
Delaware Academy of Medicine	"Sarcoidosis"	A. I. du Pont Institute	March 9, 1959
Delaware Academy of Medicine	Building Dedication	Academy of Medicine	October 13, 1959
Delaware Health Forum	"Emotional Development and Disturbances of Childhood"	P. S. du Pont School	February 24, 1959
Delaware Health Forum	"Life Stress and Bodily Disease"	P. S. du Pont School	March 24, 1959

Delaware Division, American Cancer Society	Annual Meeting	October 22, 1959
Delaware Chapter, American Heart Association	Annual Meeting	May 19, 1959
Mental Health Association of Delaware	Annual Meeting	April 30, 1959

The Journal will be pleased to receive notice of major medical meetings in this area for inclusion in this schedule.

WILLIAM N. FENIMORE**1886 - 1959**

Dr. Fenimore died on January 5th after a lengthy illness. After studying in the Wilmington Public Schools, Wilmington Friends School and Phillips Exeter Academy, he received his M. D. from Jefferson in 1921. He served in both World Wars, being a Captain in the Medical Corps in World War II. He was coroner's physician from 1932 to 1942.

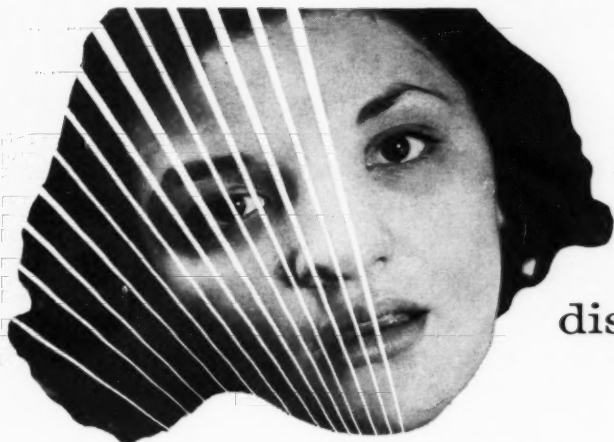
Dr. Fenimore is survived by four sons, two daughters, and twelve grandchildren.

HOWARD N. STAYTON, JR.**1914 - 1959**

Born in Wilmington, Dr. Stayton was graduated from Wilmington High School and the University of Delaware. He received his M. D. from the University of Maryland in 1940 and served his internship in the Delaware Hospital. He then practiced in Lewes and Wilmington before leaving private practice in 1951 to become physician for the Chrysler plant in Newark. He was a member of the State Board of Health from 1950 to 1952. In addition to his wife, he is survived by three daughters and a son, and his mother.

E. HUGHES NUTTER**1909 - 1959**

Dr. Nutter died on February 24th after a short illness. Born on Tangier Island, Virginia, he was a graduate of Alexis I. du Pont High School and Ohio Wesleyan College. He received his M. D. from Hahnemann Medical College in 1935. After serving his internship at the Memorial Hospital (then the Homeopathic Hospital), he practiced in Newark until the time of his death. He is survived by his wife, a daughter and a son.



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*A Symposium on the Pharmacologic Effects of Dartal on the Liver, Chicago, Searle Research Laboratories, Feb. 7, 1958.

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1. Editorial: *New England J. Med.* 258:48, 1958.

2. Vinnicombe, J.: *Antibiotic Med. & Clin. Ther.* 5:474, 1958.

3. Sheth, U. K., et al.: *Ibid.*, p. 604, 1958.

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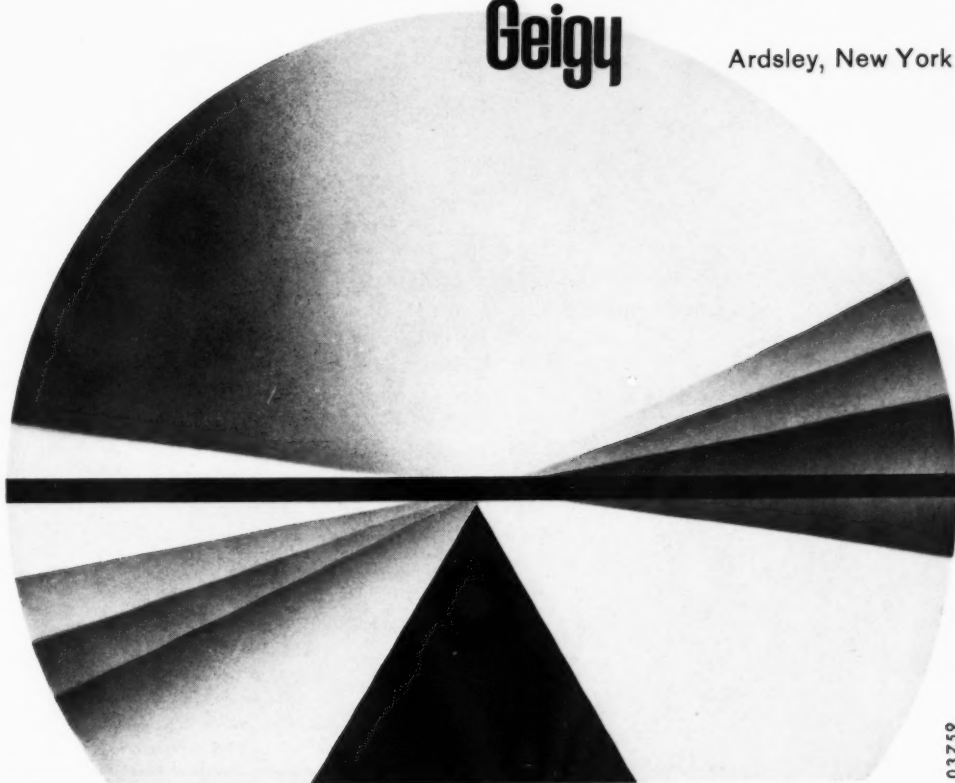
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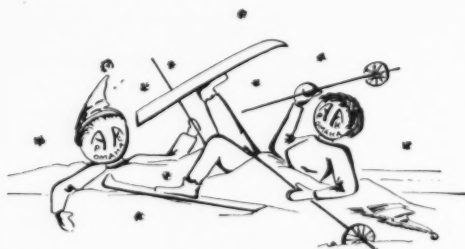


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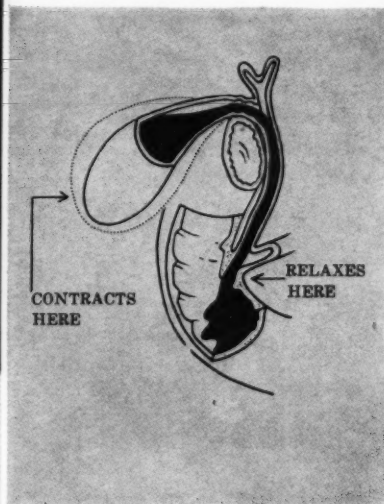
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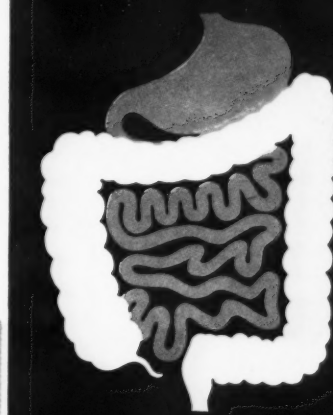
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1. Herland, A. L., Lowenstein, A.: Quart.
Rev. Surg. Obst. & Gynec. 14:196 (Dec.) 1957

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Acetylsalicylic acid	325 mg.
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References: 1. Spies, T. D., et al.: J.A.M.A. 159:645, 1955. 2. Spies, T. D., et al.: Postgrad. Med. 17:1, 1955. 3. Gelli, G., and Della Santa, L.: Minerva Pediat. 7:1456, 1955. 4. Guerra, F.: Fed. Proc. 12:326, 1953. 5. Busse, E. A.: Clin. Med. 2:1105, 1955. 6. Sticker, R. B.: Panel Discussion, Ohio State M. J. 52:1037, 1956.

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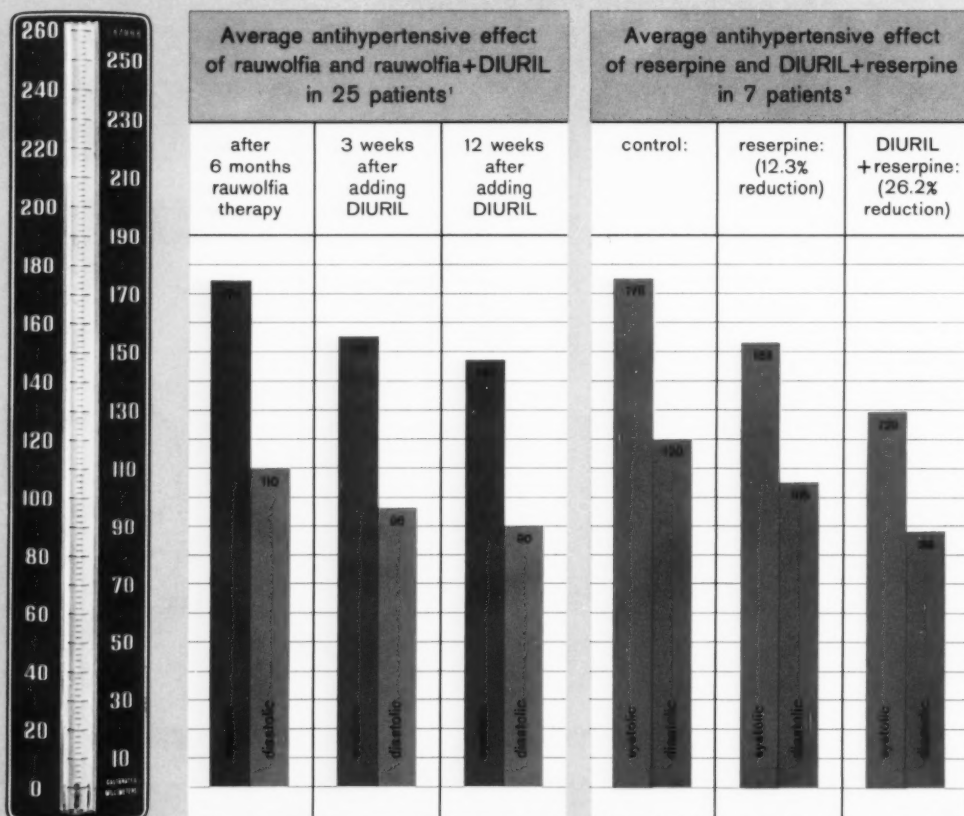
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effective therapy for most patients

DIUPRES by itself usually provides effective therapy for a majority of patients with mild or moderate hypertension, and even for many patients with severe hypertension. Many patients now treated with other agents which frequently cause distressing side effects can be adequately managed with well tolerated DIUPRES.

provides basic therapy

Should other drugs need to be added to DIUPRES, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.

rapid onset of effect

The antihypertensive action of DIUPRES is rapidly evident. (Considerable time may elapse before the antihypertensive effect of reserpine alone is observed.)

fewer and less severe side effects

DIUPRES may be expected to cause fewer and less severe side effects than are encountered with other antihypertensive therapy. (Since DIURIL and reserpine potentiate each other, the required dosage of each is usually less when given together as DIUPRES than when given alone. Such reduction in dosage makes side effects less likely to occur.)

often obviates weight gain

DIUPRES minimizes the problem of weight gain seen with reserpine (reserpine alone has been reported to produce weight gain in 50 per cent of patients).^{1,4}

virtually eliminates fluid retention

DIUPRES is not likely to cause either clinical or subclinical retention of sodium and water. (Hypotensive drugs, par-

ticularly rauwolfia⁵ and hydralazine,⁶ may cause fluid retention. Even when such retention is subclinical, their antihypertensive effectiveness is diminished.⁶)

diet more palatable

With DIUPRES, there is less need for rigid restriction of dietary salt, which patients find so burdensome.

"It may well be that the drug [DIURIL] produces the benefits of a markedly restricted low sodium diet but without its hardships."³

subjective and objective improvement

DIUPRES allays anxiety and tension, thus reducing the emotional component of hypertension. Organic changes of hypertension may be arrested and reversed. Headache, dizziness, palpitations and tachycardia are usually promptly relieved by DIUPRES. When the *anginal syndrome* accompanies hypertension, the administration of DIUPRES may also cause diminution or even disappearance of this syndrome concurrent with control of the hypertension.

convenient, controlled dosage

Instead of two separate prescriptions, you write one prescription . . . the patient takes one tablet, rather than two different tablets . . . and the dosage schedule is easier for the patient to remember and follow.

"patients have fewer lapses and make fewer mistakes in dosage, the simpler the regimen can be made. Therefore I do not hesitate to use more than one medicament combined in one tablet, provided this gives approximately the correct dosage of each."⁶

economical

DIUPRES will cost the patient less than if he were given two separate prescriptions for its components.

Indications:

DIUPRES is indicated in hypertension of all degrees of severity. It can be used in the following ways:

- as total therapy
- as primary therapy, adding other drugs if necessary
- as replacement or adjunctive therapy in patients now treated with other agents

Precautions:

The precautions normally observed with DIURIL or reserpine apply to DIUPRES. Additional information on DIUPRES is available to physicians on request.

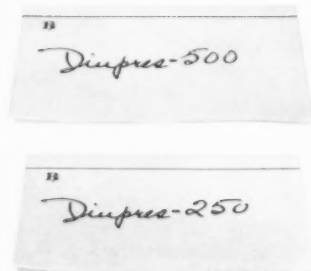
Recommended dosage range:

DIUPRES-500—one tablet one to three times a day.

DIUPRES-250—one tablet one to four times a day.

If necessary, other agents may be added.

If the patient is receiving ganglion blocking agents or hydralazine, their dosage should be cut by 50 per cent when DIUPRES is added.



DIUPRES-500

500 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine.
Bottles of 100, 1000.

DIUPRES-250

250 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine.
Bottles of 100, 1000.

the first "wide range" antihypertensive

DIUPRES

DIURIL[®] WITH RESERPINE

1. Rochelle, J. B., III, Bullock, A. C., and Ford, R. V.: Potentiation of antihypertensive therapy by use of chlorothiazide, *J.A.M.A.* 168:410, Sept. 27, 1958. 2. Freis, E. D., Wanko, A., Wilson, I. M., and Parrish, A. E.: Treatment of essential hypertension with chlorothiazide (Diuril), *J.A.M.A.* 166:137, Jan. 11, 1958. 3. Freis, E. D.: Treatment of hypertension. (Presented at the Annual Meeting of Southern Medical Association, Nov. 13, 1957.) 4. Moyer, J. H., Dennis, E., and Ford, R.: Drug therapy (Rauwolfia) of hypertension, *A.M.A. Arch. Int. Med.* 96:530, Oct. 1955. 5. Perera, G. A.: Edema and congestive failure related to administration of rauwolfia serpentina, *J.A.M.A.* 159:439, Oct. 1, 1955. 6. Wilkins, R. W.: Precautions in use of antihypertensive drugs, including chlorothiazide, *J.A.M.A.* 167:801, June 14, 1958.



MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

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1 Ladies and gentlemen: learn all about new VITERRA PEDIATRIC, a good supplement in a great new package.

2 First, see what happens when you push the metered plunger.

3 Aha! An exact 0.6 cc. comes out this spout. Never more, never less.

4 And notice — no drip, no waste, no sticky bottle.

5 On your right, see the Metered-Flow bottle's tight seal. No risk of contamination.

6 Let's take a minute to admire the formula.

7 That means no hot-weather loss of potency.

8 Now for a farewell treat, a taste of delicious, orange-y VITERRA PEDIATRIC. How will you have it — in fruit juice? On cereal? Straight from the spoon?

VITERRA® PEDIATRIC

each 0.6 cc. contains:

		M	I	R
		Infants	Children	
A (synthetic)	5000 U.S.P. Units	333%	167%	
D (Calciferol)	1000 U.S.P. Units	250%	250%	
B ₁ (Thiamine)	1 mg.	400%	133%	
B ₂ (Riboflavin)	1 mg.	167%	110%	
B ₆ (Pyridoxine)	1 mg.	11	11	
B ₁₂ (Cyanocobalamin)	1 mcg.	11	11	
C (Ascorbic Acid)	50 mg.	500%	250%	
Niacinamide	10 mg.	200%	133%	
Panthenol	2 mg.			

In a d-sorbitol base for better vitamin B₁₂ absorption
 (†Minimum daily requirement has not been established.)
 DOSAGE: 0.6 cc. or as directed by physician.
 In 50 cc. bottles

no refrigeration needed

METERED-FLOW BOTTLE

VITERRA® PEDIATRIC

ALLOW 30 SECONDS BETWEEN DISPENSINGS

Special note to doctors who took this tour:

Problems of over- and under-dosage, spillage, spoilage or leakage disappear with VITERRA PEDIATRIC's new Metered-Flow bottle. Why not consider these advantages when you recommend a vitamin supplement?



New York 17, N. Y.
 Division, Chas. Pfizer & Co., Inc.
 Science for the world's well-being

Exactly how does new Halodrin* restore the “premenopausal prime” in postmenopausal women?

Webster defines “prime” as the period of greatest health, strength, and beauty. In a woman, these are the childbearing years between puberty and menopause—the years when her hormone production is highest.

The inevitable reduction in this hormone production as she enters the menopause often results in physical discomfort in the form of hot flushes, nervousness, insomnia, or a multiplicity of other symptoms with which you are familiar. Superimposed on this physical picture is the psychic trauma brought on by this unavoidable evidence of aging. The thing that brings her to a physician is simply that she “feels bad.”

You can't make her 35 again—but the odds are good that you can make her feel like it! The secret is a combination of reassurance and hormones. The exact form and amount of the former defy objective analysis, but the latter can now be provided with scientific precision. Reduced to essentials, here is the explanation of exactly how hormones—in the form of Upjohn's new Halodrin—restore the “premenopausal prime.”

The normal premenopausal woman excretes estrogens in the urine in the form of estradiol, estrone, and estriol, in an approximate 28-day average ratio of 39:15:46. Starting with this urinary excretion of estrogens, it is possible to calculate backwards and estimate the amount of estradiol that must have been secreted endogenously in order to produce these urinary levels. This is possible because the proportion of estrogens which appears in the urine following parenteral administration has been established in castrated women.

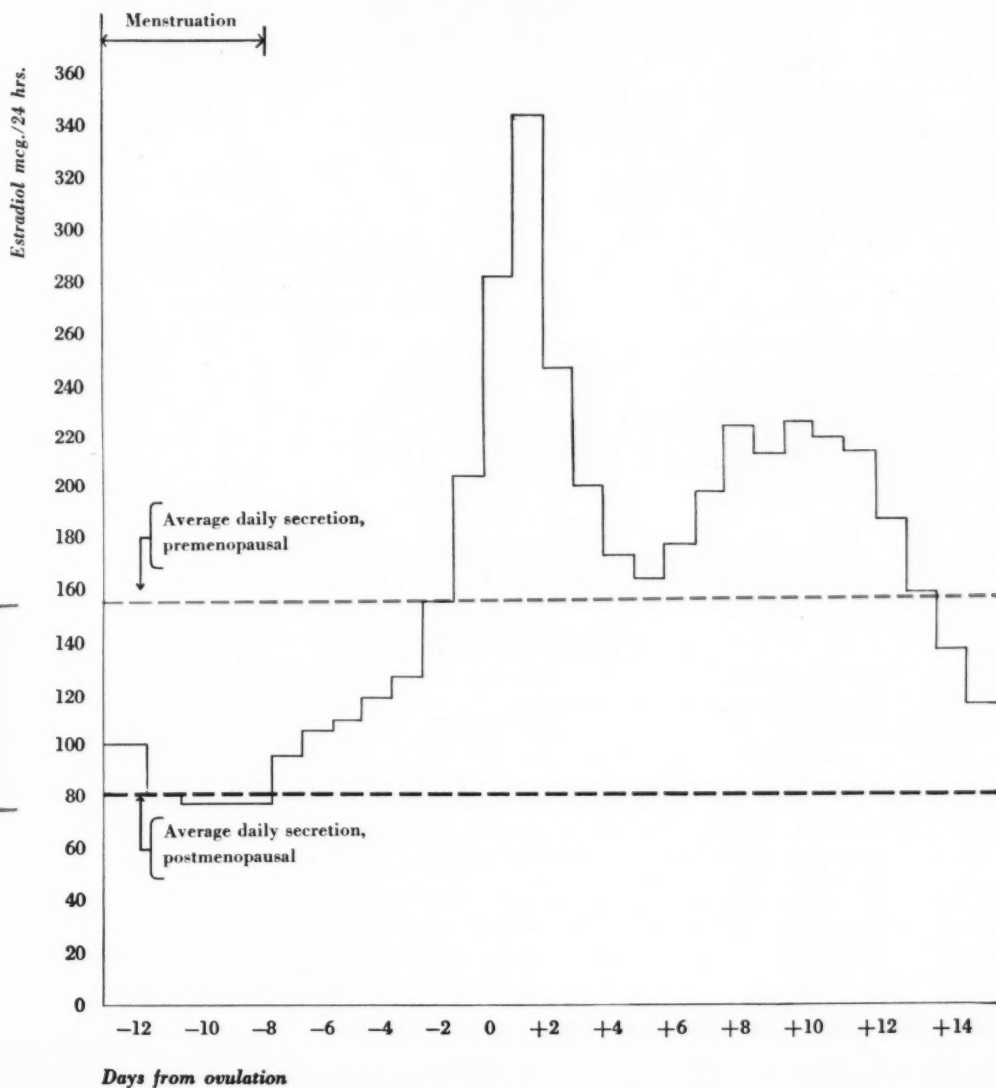
On this basis, the average endogenous output of estrogens is about 160 micrograms per day during a menstrual cycle, and 80 micrograms per day in postmenopausal women (see chart opposite). Therefore, the restoration of the “premenopausal prime” in the postmenopausal woman requires the replacement of approximately the equivalent of the 80 micrograms of estradiol per day that she no longer secretes endogenously.

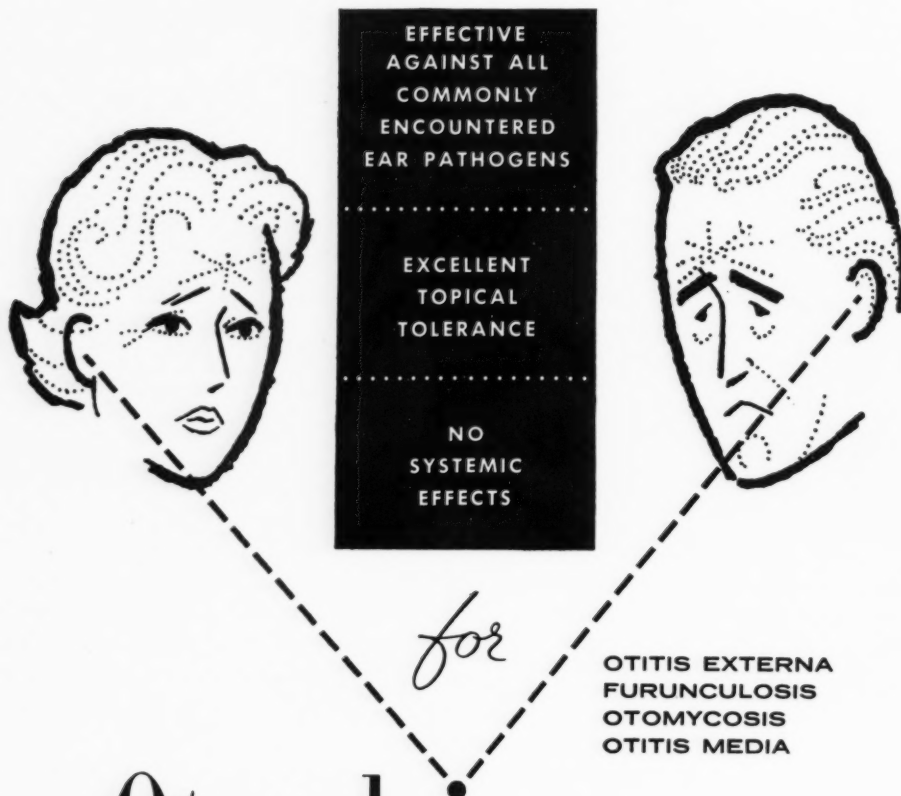
Oral ethinyl estradiol is about 2 to 2½ times as potent as parenteral estradiol. Therefore, the replacement of 80 micrograms of endogenous estradiol production per day is accomplished by the oral administration of 32 to 40 micrograms of ethinyl estradiol per day.

Each Halodrin tablet contains 20 micrograms of ethinyl estradiol, which means that the recommended dosage of 2 tablets per day provides 40 micrograms of ethinyl estradiol. This offsets the loss of 80 micrograms of endogenous estradiol production in the menopausal woman; i.e., restores the “premenopausal prime.”

Each Halodrin tablet also contains 1 mg. of Upjohn-developed Halotestin* (fluoxymesterone)—the most potent oral androgen known. The primary purpose is to “buffer” the ethinyl estradiol just enough to prevent breakthrough bleeding, which is obviously undesirable in the menopause. It also exerts other beneficial hormonal effects, one of which, in common with ethinyl estradiol, is a powerful anabolic action so desirable in patients of advanced years.

Endogenous estrogen secretion (mcg./24 hours)
(calculated from average 24-hour urinary excretion
of estradiol, estrone, and estriol)





Otamydon[®] and Otamydon[®] WITH Hydrocortisone

EAR DROPS

Manner of Use:

After gently cleansing and drying the ear canal, Otamydon (2 or 3 drops or moistened wick) is applied three or four times daily.

Supplied:

Otamydon—bottles (15 cc.) with dropper.
Otamydon \bar{c} Hydrocortisone—15 cc. combination package to be mixed prior to dispensing.

BACTERICIDAL
FUNGICIDAL
ANALGESIC
HYGROSCOPIC

Otamydon is a clear, odorless, sterile, viscid liquid containing:
Sulfamydon[®] HCl5%
Benzocaine5%
Anhydrous glycol q.s. 100

Otamydon with Hydrocortisone:
Same formula with 0.02% hydrocortisone.

Winthrop LABORATORIES
New York 18, N.Y.

re-evaluating tranquilizers?

READ WHAT CLINICIANS ARE NOW SAYING ABOUT ATARAX®

(brand of hydroxyzine)

IN GERIATRICS

"ability to decide correctly has increased, while the illogical response to anxiety has diminished."¹

IN WORKING ADULTS

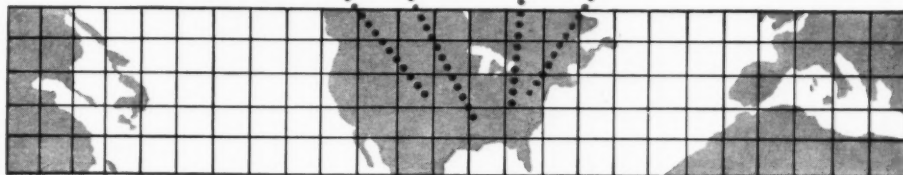
"especially well suited for ambulatory patients who must work, drive a car, or operate machinery."²

IN PEDIATRICS

"ATARAX appeared to reduce anxiety and restlessness, improve sleep patterns and make the child more amenable to the development of new patterns of behavior...."³

IN GENERAL

ATARAX is "effective in controlling tension and anxiety.... Its safety makes it an excellent drug for out-patient use in office practice."⁴



INVESTIGATORS AGREE ON OPTIMAL ATARAX DOSAGES

For childhood behavior disorders	10 mg. tablets Syrup	3-6 years, one tablet t.i.d. over 6 years, two tablets t.i.d. 3-6 years, one tsp. t.i.d. over 6 years, two tsp. t.i.d.
For adult tension and anxiety	25 mg. tablets Syrup	one tablet q.i.d. one tbsp. q.i.d.
For severe emotional disturbances	100 mg. tablets	one tablet t.i.d.
For adult psychiatric and emotional emergencies	Parenteral Solution	25-50 mg. (1-2 cc.) intramuscularly, 3-4 times daily, at 4-hour intervals. Dosage for children under 12 not established.

• **Supplied:** Tablets, bottles of 100. Syrup, pint bottles. Parenteral Solution, 10 cc. multiple-dose vials.

• **References:** 1. Smigel, J. O., et al.: J. Am. Ger. Soc., in press. 2. Freedman, A. M.: Pediatr. Clin. North America 5:573 (Aug.) 1958. 3. Ayd, F. J., Jr.: New York J. Med. 57:1742 (May 15) 1957. 4. Menger, H. C.: New York J. Med. 58:1684 (May 15) 1958. 5. Coirault, M., et al.: Presse méd. 64:2239 (Dec. 26) 1956. 6. Bayart, J.: Presented at the International Congress of Pediatrics, Copenhagen, Denmark, July 22-27, 1956.

ATARAX®



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 Science for the World's Well-Being

VARIDASE* BUCCAL TABLETS

Streptokinase-Streptodornase Lederle

Controls Inflammation and Swelling...Relieves Pain...
Promotes Healing Through Enhancement of
Fibrinolysis at the Site of Trauma or Infection.

References: 1. Innerfield, I.; Shub, H., and Boyd, L. J.: New England J. Med. 258: 1069 (May 24) 1958. 2. Miller, J. M.; Godfrey, G. C.; Ginsberg, M. J., and Papastrat, G. J.: J. A. M. A. 166:478 (Feb. 1) 1958. 3. Davidson, E.; Prigot, A., and Maynard, A. de L.: Harlem Hosp. Bull. II: 1 (June) 1958 *Reg. U. S. Pat. Off.

In Sinusitis

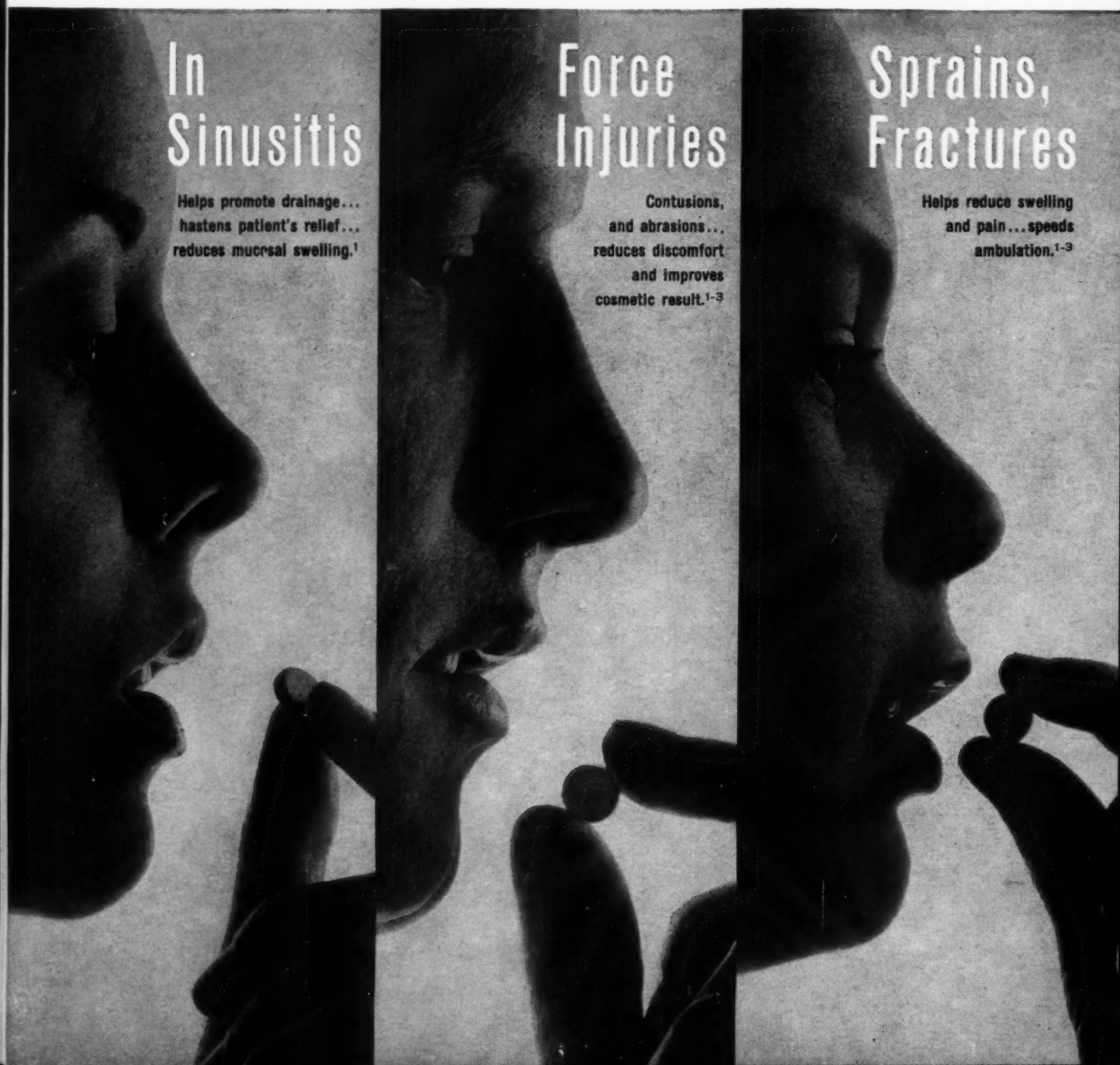
Helps promote drainage...
hastens patient's relief...
reduces mucosal swelling.¹

Force Injuries

Contusions,
and abrasions...
reduces discomfort
and improves
cosmetic result.¹⁻³

Sprains, Fractures

Helps reduce swelling
and pain...speeds
ambulation.¹⁻³



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Established Efficacy and Safety: For five years VARIDASE, in parenteral form, has been used with success in many thousands of cases. Its ability to control inflammation, swelling and associated pain, aid penetration of antibiotics, and hasten healing has been demonstrated in such conditions as severe trauma, infected ulcerations, and following extensive surgery.

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Inflammation and edema associated with: trauma and infection • cellulitis • abscess • hematoma • thrombophlebitis • sinusitis • uveitis • chronic bronchitis • leg ulcer • chronic bronchiectasis.

Each VARIDASE Buccal Tablet contains 10,000 Units Streptokinase and 2,500 Units Streptodornase.

Administration: VARIDASE Buccal Tablets should be retained in the buccal pouch until dissolved. For maximum absorption patient should delay swallowing saliva.

Dosage: One tablet four times daily for a minimum of three days. When infection is present, VARIDASE Buccal Tablets should be given in conjunction with an antibiotic such as ACHROMYCIN® V Tetracycline and Citric Acid.

Available in bottles of 24.

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Chronic Bronchitis

Loosens cough...resolves inflammation... increases antibiotic penetration.¹

Thrombophlebitis

Relieves thrombotic process, controls swelling...gives dramatic relief of pain.^{1, 2}

Skin Infections

Furuncles, carbuncles, abscesses...checks swelling and pain...hastens healing.^{1, 2}



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on the job again

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For the patient who does not require steroids

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Reciprocally acting nonsteroid antirheumatics . . . more effective than salicylate alone.

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Sodium salicylate U.S.P. 0.3 Gm. (5 gr.)
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Ascorbic acid 50.0 mg.

or for the patient who should avoid sodium

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Pabalate, with sodium salts replaced by potassium salts.

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(PABALATE WITH HYDROCORTISONE)

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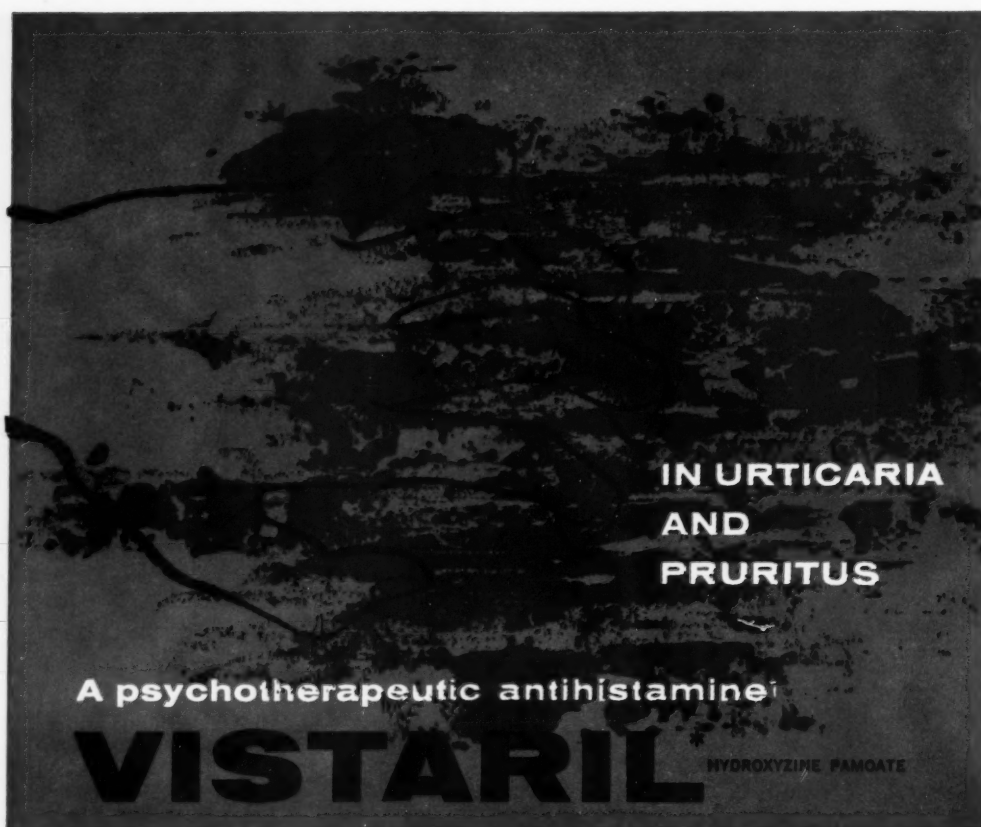
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Hydrocortisone (alcohol) 2.5 mg.
Potassium salicylate 0.3 Gm.
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A psychotherapeutic antihistamine†

VISTARIL HYDROXYZINE PAMOATE

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Specific Antihistaminic Effect
reduces—erythema, excoriation
and extent of lesions¹⁻⁴

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individual response.

References: 1. Feinberg, A. R., et al.: J. Allergy
29:358 (July) 1958. 2. Eisenberg, B. C., Clinical
Medicine 5:897-904 (July) 1958. 3. Robinson,
H. M., et al.: J.A.M.A. 161:604-606 (June 16)
1958. 4. Robinson, H. H., et al.: So. Med. J.
50:1282 (Oct.) 1957.

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Psychotherapeutic Potency
relieves—tension, anxiety
and itching.¹⁻⁴

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and 2 cc. Steraject® Cartridges, each cc.
containing 25 mg. hydroxyzine (as the HCl)

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"mycin"
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respiratory infections

prompt,
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blood levels

minimal
adverse reactions

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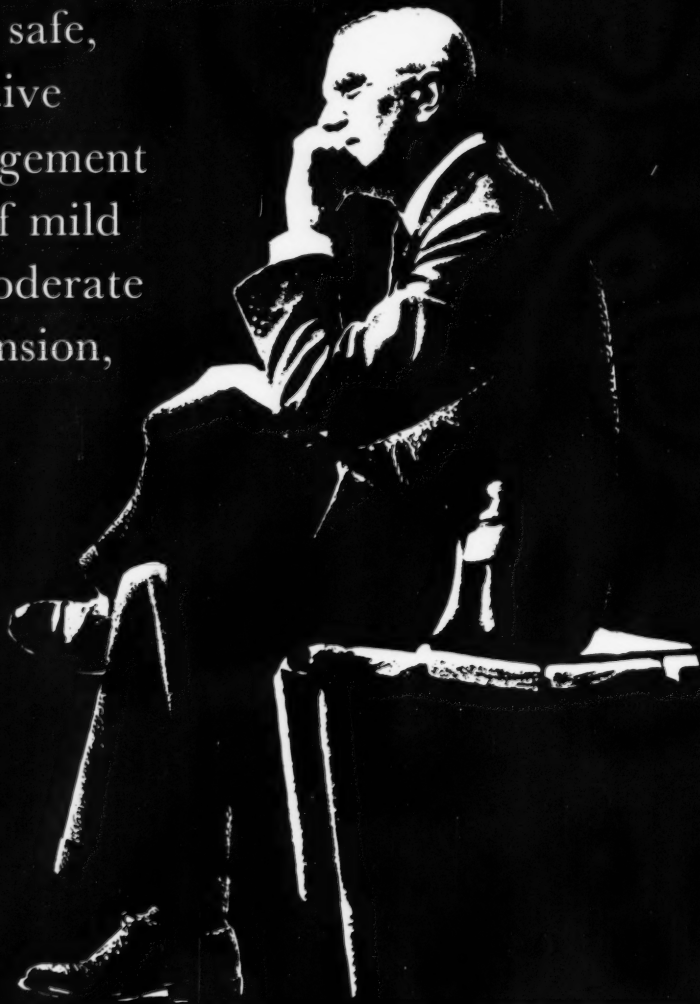


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for safe,
effective
management
of mild
to moderate
hypertension,



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Prescribed with confidence 8,863,769 times Veratrite continues to be the antihypertensive of choice for treating geriatric patients.

Veratrite effectively reduces blood pressure through action on the sympathetic nervous system, without detriment to the cardiac output.

Each VERATRITE tabule contains:

Cryptenamine (tannates) 40 C.S.R.* Units
Sodium nitrite 1 gr.
Phenobarbital ¼ gr.

*Carotid Sinus Reflex

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running noses and open stuffed noses orally

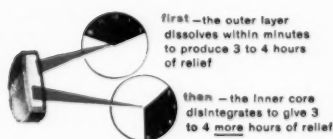
with TRIAMINIC, the oral nasal decongestant

- in nasal and paranasal congestion
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- in postnasal drip
- in allergic reactions of the upper respiratory tract

safer and more effective than topical medication

- reaches *all* respiratory membranes systemically
- avoids "nose drop addiction"
- presents no problem of rebound congestion
- provides longer-lasting relief

Relief with Triaminic is prompt and prolonged because of this special timed-release action . . . beneficial effect starts in minutes, lasts for hours.



Each TRIAMINIC Tablet provides:

Phenylpropanolamine HCl . . . 50 mg.
Pheniramine maleate . . . 25 mg.
Pyrimamine maleate . . . 25 mg.

One-half of this formula is in the outer layer, the other half is in the core.

Dosage: One tablet in the morning, mid-afternoon and in the evening, if needed.

Triaminic[®]

Also available: For the occasional patient who requires only half dosage: timed-release TRIAMINIC JUVELETS. Each Juvelet is equivalent to ½ of a Triaminic Tablet.

For those patients who prefer liquid medication: TRIAMINIC SYRUP. Each 5 ml. tsp. of this palatable syrup is equivalent to ¼ of a Triaminic Tablet.

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SPONTIN IN SERIOUS

*A Special Report from Abbott
to the Medical Profession
on a Year's Clinical Experience
with SPONTIN®*

(Ristocetin, Abbott)

In a Spanish province, a patient lay dying of endocarditis. A short wave radio appeal for SPONTIN was intercepted by a Baltimore physician. The antibiotic was immediately flown to this faraway land, and 10 days later—the patient had recovered.

In Chicago, a moribund patient had been administered 18 combinations of 10 different antibiotics without success. Involved was a hospital-acquired staphylococcal pneumonia—plus complications. SPONTIN was substituted and the patient lived.

A five-week-old infant was critically ill with staphylococcal enteritis. Treatment failures included erythromycin and chloramphenicol. Three days of SPONTIN saved this life. The list is long and impressive and it grows daily.

Recently, a study¹ was made of serious and resistant staphylococcal infections reported to Abbott Laboratories. Many of these cases had serious complicating diseases—many were moribund, or almost so, at the time SPONTIN was started. Yet, out of the 160 staphylococcal cases studied, 93 were reported cured and 38 improved after the administration of SPONTIN.

Out of the total of 251 patients with severe infections caused by gram-positive or mixed organisms, 149 were reported cured and 53 others improved. And the record for pediatric practice was every bit as good.

Additionally, SPONTIN continues to exhibit exceptional bactericidal activity against coccal infections². And, according to another study, SPONTIN provides successful short-term therapy in endocarditis³.

Only last October, at the Antibiotics Symposium in Washington, D. C., a panel of six leading antibiotic experts placed SPONTIN at the top of all other commercially-available antibiotics for treating serious staphylococcal infections. Also, six papers—all dealing with the effectiveness of ristocetin (SPONTIN®) in treating staphylococcal infections—were presented at the Symposium.

One of the most encouraging aspects of the year's literature on SPONTIN is the increasing testimony to its safety. As the months have passed and cases have accumulated by the hundreds, it has become apparent that careful attention to dosage recommendations has practically eliminated toxicity and side effects as serious obstacles to therapy. Also, recent improvements have been made in the manufacture of SPONTIN; the drug is now made from pure crystals.

A recent report⁴ in the Journal of the American Medical Association concluded, "It is our opinion that, if proper precautions are observed, ristocetin is a [well tolerated] and potent agent to employ in the treatment of staphylococcal infections." And in another study, after successfully treating 28 patients with a variety of staphylococcal infections, the authors reported⁵, "No serious complications were noted."

Few more dramatic records have been written in such a short space of time. SPONTIN has proved itself to be a good answer, perhaps the best answer at present, to the resistant staphylococcal problem—and of real value in other serious coccal infections. It may well be your answer when you're confronted with a serious infection.

Abbott

STAPHYLOCOCCAL INFECTIONS

Excerpts from Reports Read at the Antibiotics Symposium

Spontin In Treating Severe Respiratory Infections

—“In 13 of 20 patients the results were excellent, with clinical response being evident within one to four days after institution of therapy. In three additional patients, there was some degree of improvement in pneumonic processes superimposed on tuberculosis in two cases and on pulmonary neoplasm in one. In all other cases, serious antecedent pathology undoubtedly influenced the negative or equivocal response to ristocetin therapy.⁶”

Spontin In Treating Staphylococcal Infections—After successfully treating 28 patients, the authors wrote, “Ristocetin or Spontin has proved to be bactericidal and bacteriostatic, particularly for the *Staphylococcus aureus*, which is often resistant to many other antibiotics.⁵”

Spontin In Treating Seven Difficult Cases—“Ristocetin has produced excellent results in eradicating, mitigating or preventing infection in seven selected difficult cases. Six of the seven cases involved *Staphylococcus aureus* which did not respond to chemotherapy with other antibiotics.⁷”

Spontin Blood Levels In Children—“Ristocetin was administered as a single intravenous injection of 12.5 milligrams per kilogram. This resulted in serum levels ranging from 1.3 to 10.6 mcg. after two hours with a gradual fall to a level of 0.7 mcg. per cubic centimeter or less after 12 hours.⁸”

Spontin In Treating Staphylococcal Pneumonia

—“Ristocetin was used in the treatment of 24 patients with staphylococcal pneumonia, 17 of whom had failed to respond to previously administered antibiotics. Complete clearing of pneumonitis was obtained in 16 patients and significant improvement occurred in two others. Two patients died of pneumonia; four others succumbed to other lethal diseases.⁹”

Spontin In Treating Children and Adults—“Ristocetin completely controlled severe staphylococcal infections in 11 adults and six children who received adequate therapy.¹⁰”

1. Totals represent published reports and personal communications to Abbott Laboratories.
2. Sixth Annual Symposium on Antibiotics, Washington, D. C., Oct. 15, 16, 17, 1958.
3. Romansky, M. J., and Holmes, R., Successful Short-Term Therapy of Enterococcal and Staphylococcal Endocarditis with Ristocetin—Seven Patients. Preliminary Report, Antibiotics Annual, 1957-58, p. 187.
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6. Billow, F. J., et al., Clinical Observations on Ristocetin—A Preliminary Report on its Efficacy and Toxicity in 20 Unselected Severe Respiratory Infections, In Press, Antibiotics Annual, 1958-59.
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10. Terry, R. B., Ristocetin in Children and Adults, In Press, Antibiotics Annual, 1958-59.

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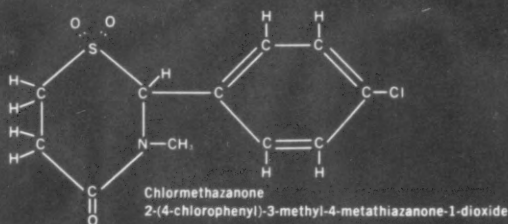
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Trancopal®

the first true tranquilaxant

Potent MUSCLE RELAXANT

and equally effective
as a TRANQUILIZER



Unrelated chemically to any other therapeutic agent in current use. Better tolerated and safer than older drugs.

for clinical results in 4092 patients

see inside

Trancopal

the first true

TRANQUILAXANT*

**Potent MUSCLE RELAXANT
and equally effective as a TRANQUILIZER**

*tran-qui-lax-ant (tran'kwi-lak'sant)
[< L. *tranquillus*, quiet; L. *laxare*, to
loosen, as the muscles]

*clinical
results in
4092⁵
patients*

Clinical Comments

“We have just started using it [Trancopal] for relaxing spastic musculature and are very much encouraged.”¹

Baker, University of
Minnesota Medical
School

“Chlormethazone [Trancopal] not only relieved *painful muscle spasm*, but allowed the patients to resume their normal activities with no interference in performance of either manual or intellectual tasks.”²

Lichtman, New York
Polyclinic Medical School
and Hospital

“The effect of this preparation in these cases [skeletal muscle spasm] was *excellent and prompt* . . .”³

Mullin and Epifano, Long
Island College Hospital

“In 120 patients with *anxiety or tension states*, 114 received satisfactory control of their condition. *Severe dysmenorrhea* and *premenstrual tension* in 65 patients refractory to the usual medications were relieved satisfactorily in 56.”⁴

Lichtman

91% Effective in Musculoskeletal Disorders

Indications

Degree of Effectiveness[†]

Low back pain (lumbago, sacroiliac)	93%
Traumatic skeletal muscle spasm	86%
Torticollis (stiff neck)	96%
Bursitis (muscle spasm)	95%
Rheumatoid arthritis (muscle spasm)	82%
Osteoarthritis (muscle spasm)	89%
Disk syndrome (muscle spasm)	98%

89% Effective in Psychogenic Disorders

Indications

Degree of Effectiveness[†]

Anxiety (tension) states	93%
Dysmenorrhea, premenstrual tension	87%
Bronchial asthma	77%

0 10 20 30 40 50 60 70 80 90 100

The results of clinical studies of over 4092 patients by 105 physicians demonstrate that Trancopal often is effective when other drugs have failed. From these studies it is clear that Trancopal probably can provide more help for a greater number of tense, spastic, and/or emotionally upset patients than any other pharmaceutical agent in current use.

[†]Excellent, good and fair

Dosage:

Usual adult dose, 1 Caplet (100 mg.) three or four times daily. Children (from 5 to 12 years), $\frac{1}{2}$ Caplet (50 mg.) three or four times daily.

Supplied:

Trancopal Caplets® (peach colored, scored) 100 mg., bottles of 100 and 1000.



Winthrop

Trancopal

the first true tranquilaxant

Potent MUSCLE RELAXANT
and equally effective
as a TRANQUILIZER

ADVANTAGES OF TRANCOPAL

- Lower incidence of side effects than with zoxazolamine, methocarbamol or meprobamate.
- No known contraindications. Blood pressure, pulse rate, respiration and digestive processes unaffected by therapeutic dosage. No effects on hematopoietic system or liver and kidney function.
- Low toxicity.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.
- No perceptible soporific effect, even in high dosage.

SUPPLIED

Trancopal Capslets (peach colored, scored)
100 mg., bottles of 100 and 1000.

REFERENCES

1. Baker, A. B.: Drugs to relieve increased tension, spasticity, and rigidity of muscles, *Modern Med.* 26:140, April 15, 1956 • 2. Lichtman, A. L.: New developments in muscle relaxant therapy, *Kentucky Acad. Gen. Pract.* 4:28, Oct., 1958. • 3. Mullin, W. G., and Epifano, Leonard: To be published. • 4. Lichtman, A. L.: To be published. • 5. Cooperative Study, Department of Medical Research, Winthrop Laboratories.

INDICATIONS

Musculoskeletal

Low back pain (lumbago)
Neck pain (torticollis, etc.)
Bursitis
Rheumatoid arthritis
Osteoarthritis
Disk syndrome
Fibrositis
Joint disorders (ankle sprain, tennis elbow, etc.)
Myositis
Postoperative myalgias

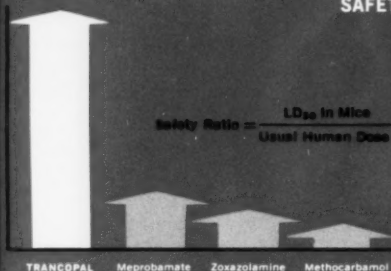
Psychogenic

Anxiety and tension states
Dysmenorrhea
Premenstrual tension
Asthma
Angina pectoris

Neurologic

Muscle spasm (in paralysis agitans, multiple sclerosis, hemiplegia, cerebral palsy)

SAFETY



Comparative pharmacologic tests showed that Trancopal is up to thirteen times as safe, or up to thirteen times less toxic. The measure of safety was the LD_{50} in mice/usual human dose.

SIDE
EFFECTS 2.3%

**Patients
without
side effects
97.7%**

**INCIDENCE OF SIDE
EFFECTS WITH TRANCOPAL
IN 4262 PATIENTS.**

Winthrop Laboratories • New York 18, N. Y.

Trancopal (brand of chlorazepate) and Capslets, trademarks reg. U. S. Pat. Off.

Printed in U. S. A. (4067A)

in corticosteroid
therapy of
allergic diseases
asthma-hay fever
allergic rhinitis
allergic dermatitis
drug reactions



Decadron^{*}

DEXAMETHASONE

to treat more patients more effectively

a new order of magnitude in therapeutic effectiveness
a new order of magnitude in margin of safety

Excellent and good-to-excellent results are reported[†] with DECADRON in nearly all of 362 patients with various allergic disorders, including a number of cases who had failed to respond to other corticosteroids. **No major reactions** were observed in these extensive clinical studies even after four months of continuous therapy—DECADRON produced no peptic ulcer, no diabetes, no significant hypertension, no sodium retention, no potassium depletion, no edema, no undesirable psychic reactions, and no unusual or new side effects. Less than five per cent of patients experienced minor reactions, none of which prevented continuing administration of DECADRON.

Moreover, several investigators report that side effects induced by previous corticosteroid therapy such as gastric

intolerance, peripheral edema, headache, vertigo, muscle weakness, ecchymoses, flushing, sweating, moon facies, hypertension, hirsutism, and acne **often disappeared during therapy with DECADRON.** [†]Analysis of clinical reports.

Dosage: One 0.75 mg. tablet of DECADRON will replace one 4 mg. tablet of methylprednisolone or triamcinolone, one 5 mg. tablet of prednisone or prednisolone, one 20 mg. tablet of hydrocortisone, or one 25 mg. tablet of cortisone.

Detailed information on dosage and precautions is available to physicians on request.

Supplied: As 0.75 and 0.5 mg. scored, pentagon-shaped tablets in bottles of 100.

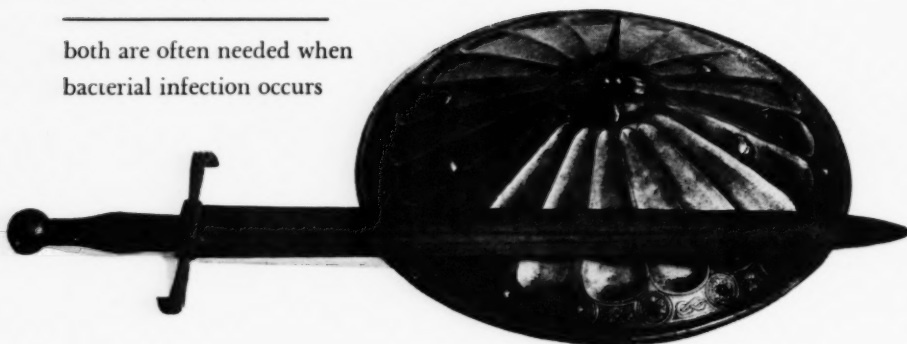
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MERCK SHARP & DOHME
DIVISION OF MERCK & CO., Inc., PHILADELPHIA 1, PA.

- prompt, aggressive antibiotic action
- a reliable defense against monilial complications

both are often needed when bacterial infection occurs



for a direct strike at infection

Mysteclin-V contains tetracycline phosphate complex

It provides a direct strike at all tetracycline-susceptible organisms (most pathogenic bacteria, certain rickettsias, certain large viruses, and *Endamoeba histolytica*).

It provides the new chemical form of the world's most widely prescribed broad spectrum antibiotic.

It provides unsurpassed initial blood levels — higher and faster than older forms of tetracycline — for the most rapid transport of the antibiotic to the site of infection.

for protection against monilial complications

Mysteclin-V contains Mycostatin

It provides the antifungal antibiotic, first tested and clinically confirmed by Squibb, with specific action against *Candida* (*Monilia*) *albicans*.

It acts to prevent the monilial overgrowth which frequently occurs whenever tetracycline or any other broad spectrum antibiotic is used.

It protects your patient against antibiotic-induced intestinal moniliasis and its complications, including vaginal and anogenital moniliasis, even potentially fatal systemic moniliasis.

MYSTECLIN-V

Squibb Tetracycline Phosphate Complex (Sumycin) and Nystatin (Mycostatin)

Capsules (250 mg./250,000 u.), bottles of 16 and 100. Half-strength Capsules (125 mg./125,000 u.), bottles of 16 and 100.

Suspension (125 mg./125,000 u. per 5 cc.) 60 cc. bottles. Pediatric Drops (100 mg./100,000 u. per cc.) 10 cc. dropper bottles.

SQUIBB



Squibb Quality — the Priceless Ingredient

*MYSTECLIN®, SUMYCIN® and MYCOSTATIN® ARE SQUIBB TRADEMARKS

Established Standard Therapy in Hypertension*

Rauwiloid[®]

alseroxylon, 2 mg.

*Because

Rauwiloid provides effective Rauwolfia action virtually free from side effects... the smooth therapeutic efficacy of Rauwiloid is associated with significantly less toxicity than reserpine... and with a lower incidence of depression. Tolerance does not develop.

Rauwiloid is initial therapy for every hypertensive patient. ...Dosage adjustment is never a problem...



just two tablets
at bedtime

After full effect
one tablet
suffices

When more potent drugs are needed, prescribe one of the *convenient single-tablet combinations*

Rauwiloid[®] + Veriloid[®]

alseroxylon 1 mg. and alkavervir 3 mg.

or

Rauwiloid[®] + Hexamethonium

alseroxylon 1 mg. and hexamethonium
chloride dihydrate 250 mg.

Many patients with severe hypertension can be maintained on Rauwiloid alone after desired blood pressure levels are reached with combination medication.

Riker

Northridge, California



"Doctor, I get so mad at everyone when I diet."

'Dexamyl' *Spansule* capsules provide single-dose daylong appetite control and an often remarkable mood improvement. A feeling of serene optimism frequently replaces the tension and irritability so characteristic of the dieting patient.

When your overweight patient is listless and lethargic, 'Dexedrine' *Spansule* capsules will, in addition to curbing appetite, provide gentle stimulation.

DEXAMYL^{*} for most overweight patients

('Dexedrine' plus amobarbital)

Tablets • Elixir • *Spansule*^{*} sustained release capsules

In listless and lethargic overweight patients—**DEXEDRINE[†]**



SMITH KLINE & FRENCH LABORATORIES

^{*}T.M. Reg. U.S. Pat. Off.

[†]T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.

